ISSN 1120-009X

Volume 19, Supplement n. 1
September 2007

Gulf Cooperation Council Practice Guidelines for the Management of Community-Acquired Pneumonia

Journal of Chemotherapy

E.S.I.F.T. srl - Firenze

Journal of Chemotherapy

Published under the auspices of the Italian Society of Chemotherapy

Founding Editor: PIERO PERITI†

Editors: TERESITA MAZZEI, ENRICO MINI, ANDREA NOVELLI

Managing Editor: MARY FORREST

INSTRUCTIONS FOR AUTHORS

If you are interested in submitting a manuscript for publication in the *Journal of Chemotherapy,* see the complete "Instructions for Authors" on our website (www.jchemother.it). For any further information and to submit manuscripts contact:

Journal of Chemotherapy
Editorial Office
Department of Pharmacology - University of Florence
Viale Pieraccini, 6 - 50139 Firenze, Italy
tel. +39-055-4271516; fax +39-055-4271280
e-mail info@jchemother.it

Journal of
Chemotherapy

Volume 19 - Supplement n. 1 - September 2007

Contents

Subscription Information: See our website: www.jchemother.it or contact:

Administrative Office

E.S.I.F.T. srl
Via Carlo del Greco, 36 - 50141 Firenze, Italy - Tel./Fax: +39055.453647

Director: Prof. Teresita Mazzei

The ***Journal of Chemotherapy*** is indexed in: Medline (Index Medicus), Current Contents/Clinical Practice®, Research Alert Direct®, Chemical Abstracts, Embase/Excerpta Medica, Biosis and is available on Adonis CD-ROM. See our website: **http://www.jchemother.it**

Authorization of the Law Court of Florence No. 3022 of the 22nd. March, 1982.

Printer «PuntoStampa» - Firenze (Italia) - September 2007

Gulf Cooperation Council CAP Working Group

INTERNATIONAL ADVISORS

Dr. Michael S. Niederman	Chairman, Department of Medicine, Winthrop University Hospital, Professor of Medicine and Vice-Chairman, Department of Medicine, SUNY at Stony Brook, New York, USA
Dr. Gary Garber	Chief, Infectious Diseases Division, Professor of Medicine, The Ottawa Hospital, University of Ottawa, Ottawa, Canada
Dr. Virginia R. Roth	Director, Infection Prevention and Control Program, Consultant Infectious Diseases, The Ottawa Hospital, University of Ottawa, Ottawa, Canada
Dr. Qanta A. Ahmed	Assistant Professor of Medicine, Division of Pulmonary Critical Care, Allergy and Sleep Medicine, Department of Medicine, Medical University of South Carolina, Charleston, S.C., USA

GCC ADVISORY BOARD

Dr. Bandar Al Knawy	Chief Medical Officer, National Guard Health Affairs, King Abdulaziz Medical City, Riyadh (KAMC-R), Saudi Arabia
Dr. Tawfik Khoja	Director General, Executive Board of the Health Ministers' Council for GCC States, Riyadh, Saudi Arabia
Dr. Ziad A. Memish	Director, GCC States Center for Infection Control and Executive Director, Infection Prevention & Control Program, King Abdulaziz Medical City, Riyadh, Saudi Arabia
Dr. Mohammed Al-Hosni	Head, Child Health Royal Hospital and Senior Consultant, Pediatric Infectious Diseases, Ministry of Health, Sultanate of Oman
Dr. Salah Alawaidy	Director Department of Communicable Diseases and Control, Ministry Of Health, Sultanate of Oman
Dr. Haifa Almoosa	Director, Infection Control Directorate, Ministry of Health, Kuwait
Dr. Huda Al Ansari	Pediatric Infectious Diseases, Sulamaniyah Hospital, Ministry of Health, Kingdom of Bahrain

ISSN 1120-009X

Ms. Laila Abdulatif Shaar	Head of Infection Control Department, Ministry of Health, United Arab Emirates
Dr. Najeeb Abdulaziz Abdullah	Head Department of Infection, Ministry of Health, Yemen
Dr. Naser Alansari	Head Department of Infection Control, Consultant Microbiologist, Hamad Medical Corporation, Ministry of Health, Doha, Qatar
Dr. Hanan H. Balkhy	Hospital Epidemiologist, Pediatric Infectious Diseases, King Abdulaziz Medical City-Riyadh Saudi Arabia
Ms. Christine Francis	Coordinator, Infection Control, King Abdulaziz Medical City-Riyadh, Riyadh, Saudi Arabia
Dr. Sahar Makki	Director General, Infection Prevention and Control Department, Ministry of Health, Riyadh, Saudi Arabia
Dr. Fahad Al Rabeeah	Consultant Infectious Diseases, Department of Medicine, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia
Dr. Mohammed H. Al-Zahrani	Pediatric Infectious Diseases, Security Forces Hospital, Riyadh, Saudi Arabia
Dr. Mansour Al Wakeel	Armed Forces Hospital, Riyadh, Saudi Arabia
Dr. Abdelrahman Al Hebrawy	Executive Board of Health Ministers' Council for GCC States, Riyadh, Kingdom of Saudi Arabia
Prof. Didier Pittet	International Advisor to the GCC Center for Infection Control, Professor of Medicine Geneva Hospital, Geneva, Switzerland

GCC CAP WORKING GROUP

KINGDOM OF SAUDI ARABIA

Central Region

Dr. Ziad A. Memish	Director, GCC States Center for Infection Control and Executive Director Infection Prevention & Control Program, King Abdulaziz Medical City, Riyadh, Saudi Arabia
Dr. Yaseen M. Arabi	Chairman, Intensive Care Medicine, King Abdulaziz Medical City, Assistant Professor, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia
Dr. Atef Shibl	Consultant, Microbiologgy, King Saud University, Riyadh, Saudi Arabia
Dr. Abdullah Al Shimemeri	President Saudi Critical Care Society, Consultant Pulmonologist, Dean of Academic Affairs, King Saud Bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia.
Dr. Fahad Alghofaili	Consultant Thoracic Surgeon, Security Forces Hospital, Ministry of Interior, Riyadh, Saudi Arabia

Dr. Majed Al Jeraisy	Head, Clinical Research Section, King Saud Bin Abdulaziz University for Health Sciences, Clinical Pharmacy Specialist, Pharmaceutical Care Department, King Abdulaziz Medical City, National Guard, Riyadh, Saudi Arabia
Dr. Hamdan Al Jahdali	Head of Pulmonary Division, Department of Medicine, King Abdulaziz Medical City, Riyadh, Saudi Arabia
Dr. Fahad Al Rabeeah	Consultant Infectious Diseases, Department of Medicine, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia
Dr. Mohammed H. Al-Zahrani	Consultant, Pediatric Infectious Diseases, Security Forces Hospital, Riyadh, Saudi Arabia
Dr. Mogbil Al Hedaithy	Consultant, Infectious Diseases, Saudi Council, Riyadh, Saudi Arabia
Dr. Mohammed Al Hajjaj	President of the Saudi Thoracic Society, Head of Pulmonary Medicine, King Saud University, Riyadh, Saudi Arabia
Dr. Khalid Kattan	Thoracic Surgeon, King Khalid University Hospital, King Saud University, Riyadh, Saudi Arabia
Dr. Maher Bazarbashi	Consultant, Pulmonary Medicine, Department of Medicine, King Faisal Specialist Hospital & Research Center, Riyadh, Saudi Arabia
Dr. Ali Al Barrak	Consultant, Infectious Diseases, Department of Medicine, Armed Forces Hospital (Ministry Of Defense & Aviation), Riyadh, Saudi Arabia
Dr. Abdulaziz Al Saif	Consultant, Pulmonary Medicine, Department of Medicine, Armed Forces Hospital (MODA), Riyadh, Saudi Arabia
Dr. Noura Khizi	Consultant and Head of Microbiology, Deputy Director of Pathology Department and Blood Bank, Armed Forces Hospital (MODA), Riyadh, Saudi Arabia
Dr. Emad Ibrahim	Consultant, Pulmonary Medicine, Department of Medicine, Dallah Hospital, Riyadh, Saudi Arabia

Western Region

Dr. Siraj O Wali	Consultant in Pulmonary and Sleep Medicine, Director of Sleep Center, King Abdulaziz Medical City, Jeddah, Saudi Arabia
Dr. Adel Khazindar	Consultant Infectious Diseases, Department of Medicine, King Abdulaziz University Hospital, Jeddah , Saudi Arabia
Dr. Javed Khan	Consultant Pulmonary Medicine, Department of Medicine, King Fahad Armed Forces Hospital, Jeddah, Saudi Arabia
Dr. Hesham Felemban	Consultant Infectious Diseases, Department of Medicine, Al Hada Armed Forces Hospital, Taif, Saudi Arabia

Eastern Region

Dr. Abdulrahman Alqurashi	President Saudi Society of Clinical Microbiology and infectious Diseases Consultant microbiologist, King Faisal University, Dammam, Saudi Arabia
Dr. Jaffar Al-Tawfiq	Consultant Infectious Diseases, Dept of Medicine, Saudi Aramco Medical Services Organization, Dahran, Saudi Arabia
Dr. Abdulaziz Al Nawasser	Consultant, Pulmonary Medicine, Department of Medicine, King Fahad Military Complex, Dammam, Saudi Arabia

Northern Region

Dr. Tariq Azraqi	Consultant, Infectious Diseases, Department of Medicine, King Khalid University Hospital, Aseer, Saudi Arabia
Dr. Mohamed Alhazmi	Department of Medicine, Ministry of Health, Gizan, Saudi Arabia

GCC STATES

Dr. Mohammed Al-Hosni,	Head, Child Health Royal Hospital and Senior Consultant, Pediatric Infectious Diseases, Ministry of Health, Sultanate of Oman
Dr. Huda Al Ansari	Pediatric Infectious Diseases, Sulamaniyah Hospital, Ministry of Health Kingdom of Bahrain
Dr. Najeeb Abdulaziz Abdullah	Head Department of Infection, Ministry of Health, Yemen
Dr. Naser Alansari	Head Department of Infection Control, Consultant Microbiologist, Hamad Medical Corporation, Ministry of Health, Doha, Qatar
Dr. Raeas Ahmed	Consultant Intensivist, Al Rashed Hospital, Dubai, United Arab Emirates
Dr. Eiman M.A.Mokaddas	Consultant Microbiologist and Chairman Microbiology Department, Faculty of Medicine, Kuwait University, Kuwait
Dr. Noura Alsewieh	Consultant Microbiologist, Faculty of Medicine, Kuwait University, Kuwait
Dr. Inaam Alobaid	Head of Medical Microbiology Unit, Head of Laboratory Department, Sabah Hospital, Ministry of Health, Kuwait.

These Guidelines are Endorsed by: GCC Center for Infection Control, Saudi Thoracic Society, Saudi Critical Care Society, Saudi Society of Clinical, Microbiology and Infectious Diseases

The contents of this supplement are the responsibility of the authors and not the Editors of the Journal of Chemotherapy.

REPRINT

Journal of Chemotherapy Vol. 19 - Supplement n. 1 (7-11) - 2007

Executive Summary of the Gulf Cooperation Council Practice Guidelines for the Management of Community-Acquired Pneumonia

Z.A. MEMISH [1] - Y.M. ARABI [2] - Q.A. AHMED [3] - A.M. SHIBL [4] - M.S. NIEDERMAN [5] AND THE GCC CAP WORKING GROUP (GCC-CAPWG)*

Departments of [1] Infection Prevention and Control, [2] Intensive Care Medicine, King Abdulaziz Medical City, Riyadh, Saudi Arabia, [3] Department of Medicine, Medical University of South Carolina, Charleston, South Carolina, USA, [4] Department of Microbiology, King Saud University Hospital, Riyadh, Saudi Arabia, [5] Department of Medicine, Winthrop-University Hospital, New York, USA.

Corresponding author: Ziad A. Memish MD, FACP, FRCPC, FIDSA, Executive Director, Infection Prevention and Control, National Guard Health Affairs and Director, GCC Center for Infection Control, King Abdulaziz Medical City, Riyadh, P.O. Box 22490, Riyadh 11426, Kingdom of Saudi Arabia and Adjunct Professor of Medicine, University of Ottawa, Ottawa, Canada. Tel. No.: +966-1-2520088 x 43718; Fax No.: +966-1-2520437.
E-mail: zmemish@yahoo.com, memish@ngha.med.sa

INTRODUCTION

The Gulf Cooperation Council (GCC) was established in 1981 as a cooperative framework of six countries including the United Arab Emirates, the Kingdom of Bahrain, the Kingdom of Saudi Arabia, the Sultanate of Oman, the State of Qatar and the State of Kuwait. This confederation was founded on a shared basis of language, religion, geography, history and economy. The Arab Republic of Yemen joined the GCC recently in the field of healthcare. The GCC Council of Health Ministers is comprised of health ministers from each of the seven member states, and convenes biannually. The goals of this council include coordination and integration of healthcare services in the GCC states by setting and developing regional policies and regulations. Considering the diversity of the healthcare infrastructure, available resources and dependency on expatriates from different educational and practice backgrounds, standardization of medical practice has become a major priority.

Community-Acquired Pneumonia (CAP) is a common cause of morbidity and mortality and is managed by different disciplines in a heterogeneous fashion. Development of consensus guidelines to standardize these wide variations in care has now become a prime objective. Guidelines on optimum treatment are now available for many diseases in many regions of the world in efforts to safeguard patients through uniform minimum standards of care [1-4].

This document was developed by the GCC CAP Working Group (GCC CAPWG), which collaborated in the review of current international and local data, and evidence related to CAP. In this process the GCC CAPWG developed evidence-based graded recommendations. Throughout, the GCC-CAPWG functioned as a committee and was comprised of actively practicing physicians from locally affiliated institutions. Clinician members were trained in multiple disciplines including infectious diseases, pulmonary medicine, critical care medicine, clinical microbiology, clinical pharmacy, and thoracic surgery. In addition, the GCC CAPWG sought out internationally acknowledged thought-leaders, specifically expert in the area of CAP literature and guidelines.

This document represents an update of the original 2002 statement on CAP, incorporating new information about bacteriology, patient stratification, diagnostic evaluation, antibiotic therapy, and prevention [5]. These guidelines are endorsed by the GCC Center for Infection Control, Saudi Society of Critical Care, Saudi Thoracic Society and the Saudi Society of Clinical Microbiology and Infectious Diseases.

The document includes four sections: (1) the rationale and scope of the guidelines; (2) the microbiology of CAP: (3) the clinical presentation and diagnostic workup of CAP; (4) management and prevention strategies [6-9]. Each section is structured to first give an international overview of each topic,

 ISSN 1120-009X

followed by local data, leading to overall recommendations, ending with plans for future data collection. The recommendations made in this document were graded based on the strength of the evidence as high-level (Level I), moderate-level (Level II), and low-level (Level III) evidence.

It is hoped that these guidelines will be an important step towards standardization of CAP care in the GCC and set the agenda for further local research in this important area.

RATIONALE OF GCC CAP GUIDELINES

(Please refer to the section on Rationale for Producing Evidence-Based Guidelines for Community-Acquired Pneumonia in the Gulf Cooperation Council, page 13)

- The GCC CAP working group recommends adopting these guidelines as standard of practice in the GCC region. (Level II evidence)
- The anticipated benefits include antibiotic use control, monitoring resistance and potentially improved patient outcome. (Level II evidence)

MICROBIOLOGY OF CAP IN THE GCC

(Please refer to the section on Microbiology of Community-Acquired Pneumonia in the Gulf Cooperation Council States, page 17)

- The GGC CAPWG considers the following to be the most common pathogens for CAP: *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella cataralis.* (Level II evidence)
- Atypical pathogens including *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae and Legionella pneumophila* should also be considered in the etiology of CAP in the GCC region. (Level II evidence)
- Considering that TB remains highly prevalent in the GCC region, any patient presenting with CAP could potentially be a case of pulmonary TB. Appropriate diagnostic tests for *Mycobacterium tuberculosis* should be considered in the proper setting if the patient presents with subacute or chronic symptoms and/or fails to respond to the standard therapy for bacterial CAP. (Level II evidence)
- Other less commonly encountered pathogens should be considered in patients with atypical presentations or non-resolving pneumonia. These uncommon pathogens include viral pathogens (such as influenza and varicella zoster viruses), methicillin-resistant *Staphylococcus aureus* (MRSA) or Q fever. (Level III evidence)
- The GCC CAPWG notes that Drug Resistant *Streptococcus pneumonia* (DRSP) is on the rise in the GCC region and recommends that physicians be familiar with both risk factors identifying at risk-populations and the local prevailing antimicrobial resistance patterns both in the patient's community and the admitting institution. (Level II evidence)
- Physicians are encouraged to enquire about recent antibiotic history prior to presentation, in order to assess the likelihood of resistant pathogens from the outset. (Level III evidence)
- The GCC CAP working group recommends that CAP bacteriology and resistance patterns be monitored locally and nationally. (Level III evidence).
- The group also recommends that related governmental agencies put in place regulations limiting antibiotic prescription to physician prescribers only. (Level III evidence).
- Multidisciplinary antimicrobial management teams within hospitals are recommended to control in - patient antimicrobial resistance. (Level III evidence)

CLINICAL PRESENTATION AND DIAGNOSTIC WORKUP FOR CAP

(Please also refer to the section on Clinical Presentation and Diagnostic Workup for Community-Acquired Pneumonia: The Gulf Cooperation Council CAP Working Group Consensus Statement, page 25)

- The distinction between the clinical presentation of 'typical' (i.e. pneumoccocal) and 'atypical' (non-pneumococcal) pneumonia is imprecise. Clinicians should rather focus on other variables such as age and co-morbidities in directing empiric therapy. (Level II evidence)
- CAP in older patients often presents with non-classical manifestations including somnolence, new anorexia, and confusion and tends to carry a worse outcome. (Level II evidence)
- CAP caused by DRSP is associated with a more aggressive course and a worse outcome, typified by suppurative complications, though these do not necessarily confer additional mortality. (Level II evidence)
- Chest radiography is recommended for all patients presenting with CAP to establish the diagnosis of pneumonia and the presence of complications, even allowing for the difficulty in interpreting chest x-rays in milder disease or in the emergency rooms. Efforts to obtain an old radiograph should always be made in order to make a comparison to determine if findings are new. (Level II evidence)

Outpatients with CAP

- For outpatients with CAP, Gram's stain and culture of sputum or blood are not required. Oxygen saturation should be assessed by pulse oximetry whenever available. (Level II evidence)

Hospitalized patients with CAP

- For hospitalized patients, Gram's stain and culture of sputum should be obtained if a drug-resistant or unusual pathogen is being considered. A good-quality sample is mandatory for informative results. Ideally all culture data, sputum or blood must be obtained prior to initiation of antibiotics. (Level II evidence)
- Assessment of gas exchange, routine blood chemistry and blood count should be performed. (Level II evidence)
- For those with severe CAP, the following tests should also be obtained: routine blood cultures and urinary antigen tests for *Legionella pneumophila* and *Streptococcus pneumoniae.* (Level II evidence)
- For mechanically ventilated patients, an endotracheal aspirate should be cultured. (Level II evidence).
- In selected, severely ill, CAP patients more aggressive diagnostic testing such as bronchoscopic sampling should be performed, to be determined on an individual basis. (Level II evidence)
- In patients with persistent productive cough, significant weight loss, night sweats, or other risk factors for tuberculosis, a sputum sample for acid-fast bacilli stain and TB cultures should be performed, and the patient kept in respiratory isolation. (Level II evidence)
- For patients with significant pleural effusion or complicated parapneumonic effusion, drainage and culture of pleural fluid may aid in obtaining etiologic diagnosis. (Level II evidence)

MANAGEMENT AND PREVENTION STRATEGIES FOR CAP

(Please also refer to the section on Management and Prevention Strategies for Community Acquired Pneumonia in the Gulf Cooperation Council, page 33)

The admission and site of care decisions

- The decision to admit the CAP patient should be reserved for those deemed at higher risk of mortality based on severity assessment. CRB-65 should be used in outpatients and CURB-65 for hospitalized patients. In general, hospitalization is recommended for patients with CURB-65 score of ≥ 2 and ICU admission is recommended for those with score of ≥ 3. (Level II evidence)
- The CURB-65 is an excellent tool to avoid overlooking severe illness. However, these rules only compliment and never replace clinical judgment. (Level II evidence)
- Admission to an ICU is required for patients with septic shock requiring vasopressors or with acute respiratory failure requiring intubation and mechanical ventilation. ICU care may also be needed for patients who have multiple other criteria of potentially severe illness (hypoxemia, multilobar infiltrates, hypotension, confusion, leucopenia or thrombocytopenia). (Level II evidence)
- Patients with suspected tuberculosis should be placed under respiratory isolation immediately on admission and until TB is excluded. (Level II evidence)

Patient stratification and empiric therapy

- The central goal of these guidelines is to provide the practicing physician with an approach to the *initial antimicrobial management* of CAP. It should be mentioned that treatment guidelines are empiric in nature and antibiotics should be started as soon as possible, but always within 6 hours of presentation. Once the causative pathogen is isolated and antibiotic susceptibility testing results are known, the antibiotic regimen should be tailored accordingly. (Level II evidence)
- DRSP risks include age above 65 years, recent β-lactam therapy (within 3 months), alcoholism, immune suppression (including steroids), multiple medical co-morbidities, and exposure to children in day care facilities. Gram-negatives must be considered in the setting of underlying cardiopulmonary disease, multiple medical co-morbidities, and also recent antibiotic therapy (no specified time frame). CAP caused by *Pseudomonas aeruginosa* must be considered when structural lung disease is present, for example in those with bronchiectasis, current or recent corticosteroid use (>10 mg prednisone/day), prior broad-spectrum antibiotics for >7 days within the past month and malnutrition. (Level II evidence)
- These guidelines are based on an assessment of place of therapy (outpatient, hospital ward, or ICU) and the presence of modifying factors. These modifying factors include the presence of the risk factors for DRSP, the presence of risk factors for enteric gram-negative bacilli, and the presence of risk factors for *P. aeruginosa.* 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. Once hospitalization occurs, DRSP risks must always be considered, both in the ward patient and in the ICU. The diagnostic work up remains unchanged, and no evidence exists that the suspicion of DRSP should require additional testing. Atypical pathogen infection should be considered in all patient groups, sometimes in the form of mixed infection. (Level II evidence)

– The issue of using of fluoroquinolones as a first line therapy for CAP in the settings of high prevalence of tuberculosis was specifically discussed by the GCC CAPWG. Consensus held fluoroquinolones suitable for first line therapy in CAP in the general population. However, in CAP patients presenting with features suggestive of tuberculosis or in patients who failed to respond rapidly to CAP therapy, fluoroquinolones should be avoided. If inadvertently used in this setting, these drugs can mask the diagnosis of tuberculosis, delaying proper treatment. (Level III evidence)

Outpatient therapy

– The outpatient with no modifying risks or comorbidities can be treated as an outpatient with a single advanced generation macrolide, which would include azithromycin and clarithromycin. (Level II evidence)
– If the patient is intolerant of macrolides or macrolide-allergic, doxycycline is a second choice, as its anti-pneumococcal activity ranks lower. (Level II evidence)
– A 2.0 gram single dose of the newly licensed extended released azithromycin can be used in mild to moderate CAP. (Level II evidence)
– The outpatient with modifying factors should receive monotherapy with a respiratory fluoroquinolone or a β lactam with an advanced generation macrolide. (Level II evidence)

Inpatient therapy

– For CAP patients admitted to the ward, empiric treatment with respiratory fluoroquinolone monotherapy or a third-generation cephalosporin with a macrolide is recommended. (Level II evidence)
– Monotherapy with intravenous azithromycin is as effective as a traditional β-lactam/macrolide combinations in select patients. (Level II evidence)
– Risks for anaerobic infection should be covered with appropriate agents. Lung abscess, if documented, should be treated with clindamycin or metronidazole and a thoracic surgical opinion obtained when indicated. (Level III evidence)
– For CAP ICU patients without pseudomonal risk factors, the recommended antimicrobial treatment is a combination of a β-lactam plus a respiratory fluoroquinolone or a macrolide. (Level II evidence)
– Respiratory fluoroquinolone monotherapy is not recommended for ICU-admitted patients, as efficacy data in this population are lacking; most of the trials were not conducted in the critically ill CAP patient. (Level II evidence)
– When pseudomonal risk factors exist, two antipseudomonal agents from different classes should be used, in addition to coverage for DRSP and atypical pathogens. These two requirements can be met with the selected beta lactams as piperacillin-tazobactam, cefepime or carbapenems. Additional agents should be added to these drugs and could include either an anti-pseudomonal quinolone (ciprofloxacin or levofloxacin), or the combination of an aminoglycoside plus a macrolide or anti-pneumococcal quinolone (levofloxacin or moxifloxacin). (Level II evidence)
– CAP due to MRSA should be suspected in patients with severe CAP or post-influenza CAP and anti MRSA agents, such as vancomycin or linezolid must be added. If vancomycin is used, consideration should be given to adding clindamycin to limit toxin production. (Level II evidence)
– Short-course antibiotic therapy is equivalent to standard length of therapy for clinical cure and bacterial eradication. Adults should be treated for a minimum of 5 days, should be afebrile for 48-72 hours and have no signs of clinical instability before discontinuing therapy. (Level II evidence)

Natural history of CAP

– Normal resolution of pneumonia is not easily defined and varies according to the underlying etiology. Most patients report subjective improvement within 3 to 5 days of initiation of therapy. However, radiologic improvement usually lags behind clinical improvement. Early responders who can tolerate oral therapy should be changed to oral therapy (typically by the third day of parenteral therapy) as long as they show clinical stability. (Level II evidence)

CAP during Hajj

– The GCC CAPWG recommends influenza vaccination to all pilgrims attending Hajj, especially those with underlying chronic illnesses such as cardiopulmonary disease. Influenza vaccination is also mandatory for all healthcare workers in Makkah and Madinah, the sites of worship during the Hajj. (Level II evidence)
– The GCC CAPWG recommends the use of facemasks during Hajj, to reduce airborne transmission of disease. (Level III evidence)
– In treatment of CAP during Hajj, the use of fluoroquinolones as a first line therapy should be avoided because of concerns of masking and delaying tuberculosis diagnosis. (Level III evidence)

Prevention and control

– The GCC CAPWG adopts the recommendations of the Advisory Committee on Immunization Practices (ACIP) for annual administration of inactivated influenza vaccine for persons at high risk

for influenza-related complications and severe disease, including persons of any age with certain chronic medical conditions, persons aged ≥50 years, pregnant women, persons who live with or care for persons at high risk (household contacts) and health-care workers. (Level II evidence)

- In addition, influenza vaccine is recommended for adults who are going to perform Hajj and Umrah. (Level III evidence)
- Pneumococcal polysaccharide vaccine is recommended for specific high risk groups including chronic cardiovascular, renal or liver disease, cerebrospinal fluid leaks, asplenia, immunocompromised conditions, long term care facility residents and specifically for chronic pulmonary disease and diabetes mellitus patients. (Level II evidence)
- Varicella-Zoster Virus (VZV) vaccine is recommended for susceptible adults to VZV infection. (Level II evidence)
- Considering the high prevalence of TB in the region, strict adherence to the international guidelines for prevention of spread of TB must be observed at all times. (Level II evidence)

REFERENCES

[1] Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44 Suppl 2: S27-72.

[2] Hedlund J, Stralin K, Ortqvist A, Holmberg H. Swedish guidelines for the management of community-acquired pneumonia in immunocompetent adults. Scand J Infect Dis 2005; 37 (11-12): 791-805.

[3] Woodhead M, Blasi F, Ewig S, Huchon G, Ieven M, Ortqvist A, et al. Guidelines for the management of adult lower respiratory tract infections. Eur Respir J 2005; 26(6): 1138-80.

[4] BTS Guidelines for the Management of Community Acquired Pneumonia in Adults. Thorax 2001;56 Suppl 4: IV1-64.

[5] Memish ZA, Shibl AM, Ahmed QA. Guidelines for the management of community-acquired pneumonia in Saudi Arabia: a model for the Middle East region. Int J Antimicrob Agents 2002;20 Suppl 1: S1-12.

[6] Memish Z, Ahmed QA, Arabi YM, Shibl A, Niederman M. Rationale for producing evidence-based guidelines for community-acquired pneumonia in the Gulf Cooperation Council, J Chemother 2007; 19, suppl n 1: 13-16

[7] Memish Z, Ahmed QA, Arabi YM, Shibl A, Niederman M. Microbiology of community acquired pneumonia in the Gulf Cooperation Council States. J Chemother 2007; 19, suppl n 1: 17-23

[8] Memish Z, Arabi YM, Ahmed QA, Al Jahdali H, Shibl A, Niederman M. Clinical presentation and diagnostic workup for community acquired pneumonia: The Gulf Cooperation Council CAP Working Group Consensus Statement. J Chemother 2007;19, suppl n. 1: 25-31

[9] Memish Z, Arabi YM, Ahmed QA, Shibl A, Niederman M. Management and prevention strategies for community acquired pneumonia in the Gulf Cooperation Council. J Chemother 2007; 19, suppl n 1: 33-46

REPRINT

Journal of Chemotherapy Vol. 19 - Supplement n. 1 (13-16) - 2007

Rationale for Producing Evidence-Based Guidelines for Community-Acquired Pneumonia in the Gulf Corporation Council

Z.A. MEMISH [1] - Q.A. AHMED [3] - Y. ARABI [2] - A.M. SHIBL [4] - M.S. NIEDERMAN [5]
AND THE GCC CAP WORKING GROUP (GCC-CAPWG)

Departments of [1] Infection Prevention and Control, [2] Intensive Care Medicine, King Abdulaziz Medical City, Riyadh, Saudi Arabia, [3] Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, Department of Medicine, Medical University of South Carolina, S.C., USA, [4] Department of Microbiology, King Saud University Hospital, Riyadh, Saudi Arabia, [5] Department of Medicine, Winthrop-University Hospital, New York, USA

Corresponding author: Ziad A. Memish MD, FACP, FRCPC, FIDSA, Executive Director, Infection Prevention and Control, National Guard Health Affairs and Director, GCC Center for Infection Control, King Abdulaziz Medical City, Riyadh, P.O. Box 22490, Riyadh 11426, Kingdom of Saudi Arabia and Adjunct Professor of Medicine, University of Ottawa, Ottawa, Canada. Tel. No.: +966-1-2520088 x 43718; Fax No.: +966-1-2520437. E-mail: zmemish@yahoo.com, memish@ngha.med.sa

Summary

World-wide community-acquired pneumonia (CAP) is a common respiratory tract infection and is now a growing public health concern in the GCC region. Practice guidelines are derived statements which lead to informed clinical decision making. National and regional guidelines have been developed in North America, South America, South Africa and Western Europe to assist practitioners managing patients with CAP and have demonstrated to improve patients outcome. Four years have elapsed since the publication of the Saudi Arabian CAP guideline and notable changes in the area of CAP demand revision of this earlier document. We expanded previous guidelines to a regional level in a number of ways: by incorporating changes in antimicrobial resistance profiles in the region, by considering the regional availability of antibiotics and diagnostic procedures, by including emerging data on new advancements in diagnosis and treatment of CAP and, finally, by adopting an evidence-based approach in grading relevant data.

The current document seeks to target primary care physicians who manage most patients with CAP in the GCC region. All available and relevant peer-reviewed studies published until June 2007 were considered in the literature review. Based on the strength of the evidence, we graded our recommendations to high-level (Level I), moderate-level (Level II), and low-level (Level III) evidence.

Key words: **Guidelines, pneumonia, community acquired infection, Saudi Arabia, evidence-based medicine.**

INTERNATIONAL PERSPECTIVE

Community-acquired pneumonia (CAP) remains a substantial cause of morbidity and mortality world-wide [1]. National and regional guidelines have been developed in North America, South America, South Africa and Western Europe to assist practitioners managing patients with CAP [2-12]. By consolidating large amounts of information into one document and defining the strength of existing data (evidence

 ISSN 1120-009X

grading), guidelines become rapid-access and relevant references at the bedside. Guidelines delineate accepted standards of care against which current practice may be evaluated, exposing important defects in existing knowledge, and, eventually, directing future research to close these gaps. However, the single most important reason to publish guidelines is in an effort to improve patient outcomes [13-18], consistently demonstrated in outcomes literature.

Simply writing guidelines alone is insufficient to change existing practice - it is the intensity of their implementation which is critical to impacting physician practice and, in turn, patient outcomes. Education alone about guidelines is probably not enough. Yealy *et al* [19] conducted a cluster-randomized trial of 32 emergency departments and 3219 CAP patients. Guideline implementation strategies were defined as low (n = 8), moderate (n = 12), and high intensity (n = 12). High intensity implementation included real-time reminders, doctor audit and feedback, intense continuous quality improvement *PLUS* education. Both moderate-intensity and high-intensity guideline implementation strategies safely increased the proportion of low-risk patients with pneumonia who were treated as outpatients. The high-intensity strategy was most effective for increasing the performance of the recommended processes of care for outpatients and inpatients.

Guidelines can be an excellent resource guiding the clinician at treatment outset but they must be utilized as such - as *guidelines*, not as 'commandments'. Clinical acumen of an experienced clinician complements and, on occasion, *overrides* guideline recommendations; used together, each tool amplifies the other. When implementing guidelines successfully, it is vital to underline this point to avoid alienating clinicians who may otherwise feel devalued or marginalized by documents from invisible panels of 'experts' leading to greater resistance toward successful guideline implementation and desired behavior change.

LOCAL PERSPECTIVE

CAP is a major outpatient and admitting diagnosis throughout the Gulf Cooperation Council (GCC) countries [1]. The GCC States include the Kingdom of Saudi Arabia, the Kingdom of Bahrain, State of Qatar, State of Kuwait, the United Arab Emirates, Sultanate of Oman and Yemen Arab Republic. This document follows recent changes instigated by the implementation of earlier guideline documents in the Middle East [20] and the 2005 development of the new GCC Center for Infection Control in Riyadh, Saudi Arabia and represents the first regional CAP guidelines to emerge from the Middle East. Four years have elapsed since the publication of the Saudi Arabian CAP guideline [20] and notable changes in the area of CAP demand revision of this earlier document. The current document seeks to target primary care physicians who manage most patients with CAP in the GCC regions. We expanded previous guidelines to a regional level in a number of ways: by incorporating changes in antimicrobial resistance profiles in the region, by considering the regional availability of antibiotics and diagnostic procedures, by including emerging data on new advancements in diagnosis and treatment of CAP and, finally, by adopting an evidence-based approach in designing these guidelines.

In keeping with recent guidelines for healthcare-associated pneumonia (HCAP), certain patient groups which were once considered within the provenance of CAP (including patients from nursing homes presenting with pneumonia) are now excluded and therefore also excluded from commentary in the current document. We justify this since distinct pathogens [predominantly Gram-negative organisms and possibly methicillin-resistant *Staphylococcus aureus* (MRSA)] are now seen in the nursing home setting, separating lower respiratory tract infections in this population clearly apart from the majority of CAP patients. In addition, the role of atypical pathogens in this patient group remains uncertain.

This document was developed by the GCC CAP Working Group (GCC CAPWG) which collaborated in the review of current local practice, regional and international data and evidence grading during serial meetings. The first meeting was conducted in Riyadh, Saudi Arabia in 2005. The GCC-CAPWG functioned as a committee and was comprised of actively practicing physicians from locally-affiliated institutions. Clinician members were trained in multiple disciplines including infectious diseases, pulmonary medicine, critical care medicine, clinical microbiology, clinical pharmacy, and thoracic surgery. Additionally, the GCC CAPWG sought out internationally-acknowledged thought-leaders, specifically expert in the area of CAP literature. Through their perspective, these experts provided invaluable context, assessment of regional and local observation and experienced assistance in the most crucial aspect of guideline development: evidence grading. This multidimensional approach combining local, regional and international expertise strengthens the final document into a mature tool.

Core members of the GCC CAPWG developed an initial draft document, which was circulated to all members in 2005. The committee reconvened in 2006 in Dubai, United Arab Emirates where the draft guidelines were presented and discussed. Definitive recommendations were extracted from this exercise. The guidelines were finalized and updated in June 2007 and were circulated to all members for approval. This final statement represents the majority consensus achieved through this stepwise process.

The grading system for our evidence-based recommendations is similar to the one used in the

American Thoracic Society (ATS) Community-Acquired Pneumonia (CAP) statement [4], and the definitions of high-level (Level I), moderate-level (Level II), and low-level (Level III) evidence are summarized in *Table 1*. All available and relevant peer-reviewed studies published until June 2007 were considered in the literature review. Much of the literature is observational, and only a few therapy trials have been conducted in a prospective, randomized fashion limiting the selected evidence.

TABLE 1 - *Evidence-based grading system used to rank recommendations*

Evidence Level	Definition
Level I (high)	Evidence based on well conducted, randomized controlled trials
Level II (moderate)	Evidence based on well designed, non-randomized controlled trials (including cohort and case-control studies).
Level III (low)	Evidence based on case studies, expert opinion and antibiotic susceptibility data without clinical observations

This document will describe the etiology of CAP, current issues in the region relating to antibiotic resistance, the clinical presentation of CAP, the diagnostic workup and the specific challenges of patient risk stratification. Ultimately algorithms of therapy are proposed. A section on preventative strategy was also added to this document.

RECOMMENDATIONS

Based on existing international evidence (Level II evidence), the GCC CAP working group recommends adopting these guidelines as standard of practice in the GCC region. The anticipated benefits include antibiotic use control, monitoring resistance and potentially improved patient outcome.

FUTURE DATA AND VALIDATION

CAP will be more prevalent in the future as the management of chronic diseases improves, as the number of patients with structural lung disease increases and as more of the population lives with immunosuppression [14,21]. These patterns will be magnified in GCC countries because of rising life expectancies in parallel with the economic growth of recent decades enabling health care systems to provide state of the art medical intervention. This increasing prevalence of CAP behooves the region to respond with clear and concise management guidelines for what is going to become a more commonly encountered clinical problem. Therefore, the GCC CAP group recommends the development of a regional database for CAP, which will be used for documenting the frequency with which guidelines are followed and their impact of patient outcome.

REFERENCES

[1] Al-Muhairi S, Zoubeidi T, Ellis M, Nicholls MG, Safa W, Joseph J. Demographics and microbiological profile of pneumonia in United Arab Emirates. Monaldi Arch Chest Dis 2006;65(1):13-8.

[2] Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007;44 Suppl 2:S27-72.

[3] Miyashita N, Matsushima T, Oka M. The JRS guidelines for the management of community-acquired pneumonia in adults: an update and new recommendations. Intern Med 2006;45(7):419-28.

[4] Niederman MS, Mandell LA, Anzueto A, Bass JB, Broughton WA, Campbell GD, et al. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 2001;163(7):1730-54.

[5] Gialdroni Grassi G, Bianchi L. Guidelines for the management of community-acquired pneumonia in adults. Italian Society of Pneumology. Italian Society of Respiratory Medicine Italian Society of Chemotherapy. Monaldi Arch Chest Dis 1995;50(1):21-7.

[6] Hedlund J, Stralin K, Ortqvist A, Holmberg H. Swedish guidelines for the management of community-acquired pneumonia in immunocompetent adults. Scand J Infect Dis 2005;37(11-12):791-805.

[7] [Portuguese Respiratory Society guidelines for the management of community-acquired pneumonia in immunocompetent adults]. Rev Port Pneumol 2003;9(5):435-61.

[8] BTS Guidelines for the Management of Community Acquired Pneumonia in Adults. Thorax 2001;56 Suppl 4:IV1-64.

[9] Woodhead M, Blasi F, Ewig S, Huchon G, Ieven M, Ortqvist A, et al. Guidelines for the management of adult lower respiratory tract infections. Eur Respir J 2005;26(6):1138-80.

[10] Mandell LA, Bartlett JG, Dowell SF, File TM, Jr., Musher DM, Whitney C. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis 2003;37(11):1405-33.

[11] Oliveira AG. Current management of hospitalized community acquired pneumonia in Portugal. Consensus statements of an expert panel. Rev Port Pneumol 2005;11(3):243-82.

[12] Niederman MS. Principles of appropriate antibiotic use. Int J Antimicrob Agents 2005;26 Suppl 3:S170-5.

[13] Malone DC, Shaban HM. Adherence to ATS guidelines for hospitalized patients with community-acquired pneumonia. Ann Pharmacother 2001;35(10):1180-5.

[14] Alves DW, Kennedy MT. Community-acquired pneumonia in casualty: etiology, clinical features, diagnosis, and management (or a look at the "new" in pneumonia since 2002). Curr Opin Pulm Med 2004;10(3):166-70.

[15] Campbell SG, Patrick W, Urquhart DG, Maxwell DM, Ackroyd-Stolarz SA, Murray DD, et al. Patients with community acquired pneumonia discharged from the emergency department according to a clinical practice guideline. Emerg Med J 2004; 21(6): 667-9.

[16] Hagaman JT, Yurkowski P, Trott A, Rouan GW. Getting physicians to make "the switch": the role of clinical guidelines in the management of community-acquired pneumonia. Am J Med Qual 2005; 20(1): 15-21.

[17] Dean NC, Silver MP, Bateman KA, James B, Hadlock CJ, Hale D. Decreased mortality after implementation of a treatment guideline for community-acquired pneumonia. Am J Med 2001; 110(6): 451-7.

[18] Menendez R, Torres A, Zalacain R, Aspa J, Martin-Villasclaras JJ, Borderias L, et al. Guidelines for the treatment of community-acquired pneumonia: predictors of adherence and outcome. Am J Respir Crit Care Med 2005; 172(6): 757-62.

[19] Yealy DM, Auble TE, Stone RA, Lave JR, Meehan TP, Graff LG, et al. Effect of increasing the intensity of implementing pneumonia guidelines: a randomized, controlled trial. Ann Intern Med 2005; 143(12): 881-94.

[20] Memish ZA, Shibl AM, Ahmed QA. Guidelines for the management of community-acquired pneumonia in Saudi Arabia: a model for the Middle East region. Int J Antimicrob Agents 2002; 20 Suppl 1: S1-12.

[21] Hebert PL, McBean AM, Kane RL. Explaining trends in hospitalizations for pneumonia and influenza in the elderly. Med Care Res Rev 2005; 62(5): 560-82.

REPRINT

Journal of Chemotherapy Vol. 19 - Supplement n. 1 (17-23) - 2007

Microbiology of Community-Acquired Pneumonia in the Gulf Corporation Council States

Z.A. MEMISH [1] - Q.A. AHMED [3] - Y.M. ARABI [2] - A.M. SHIBL [4] - M.S. NIEDERMAN [5]
AND THE GCC CAP WORKING GROUP (GCC-CAPWG)

Departments of [1] Infection Prevention and Control, [2] Intensive Care Medicine, King Abdulaziz Medical City, Riyadh, Saudi Arabia, [3] Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, Medical University of South Carolina, S.C., USA, [4] Department of Microbiology, King Saud University Hospital, Riyadh, Saudi Arabia, [5] Department of Medicine, Winthrop-University Hospital, New York, USA

Corresponding author: Ziad A. Memish MD, FACP, FRCPC, FIDSA, Executive Director, Infection Prevention and Control, National Guard Health Affairs and Director, GCC Center for Infection Control, King Abdulaziz Medical City, Riyadh, P.O. Box 22490, Riyadh 11426, Kingdom of Saudi Arabia and Adjunct Professor of Medicine, University of Ottawa, Ottawa, Canada. Tel. No.: +966-1-2520088 x 43718; Fax No.: +966-1-2520437.
E-mail: zmemish@yahoo.com, memish@ngha.med.sa

Summary

In spite of advances in microbiological and serological investigations over the last two decades, etiological attribution remains difficult in community-acquired pneumonia (CAP). Even after exhaustive investigation, the etiology of CAP remains unknown in up to 50% of patients. Common pathogens include *Streptococcus pneumoniae, Haemophilus influenzae* and *Moraxella catarrhalis*. In addition, several investigators document the importance of atypical pathogens including *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae and Legionella pneumophila* in the etiology of CAP in the GCC region. Increasingly, other etiologies, particularly influenza viruses, varicella zoster virus and *Mycobacterium tuberculosis*, have been recognized as causative pathogens of CAP within the region. Rates of antimicrobial resistance of *S. pneumoniae* and other pathogens are rising in the Gulf Corporation Council (GCC) region and susceptibility profiles of antibiotics against intracellular pathogens such as *Chlamydophila pneumoniae* and *Mycoplasma pneumoniae* are not routinely performed. Injudicious prescribing and over-use of antibiotics drive much resistance. The GCC CAPWG calls for urgent governmental regulations to limit and monitor antibiotic prescription in the GCC region.

Key words: **Microbiology, antibiotic, resistance, guidelines, pneumonia, community acquired infection, Saudi Arabia, evidence-based medicine.**

ETIOLOGY OF COMMUNITY-ACQUIRED PNEUMONIA (CAP): INTERNATIONAL PERSPECTIVE

Most cases of CAP are caused by a limited number of pathogens. Emerging pathogens including, Severe Acute Respiratory Syndrome (SARS)-associated coronavirus and avian influenza H5N1 [1] are beyond the scope of this document. *Streptococcus pneumoniae* is the most frequently isolated pathogen. Other bacterial causes include *Haemophilus influenzae* and *Moraxella catarrhalis* and *Staphylococcus aureus* which causes CAP especially during an influenza outbreak. The emergence of MRSA [2-7] as a cause of CAP is of a great concern. The "atypical" organisms, including *Mycoplasma pneumoniae and Chlamydophila pneumoniae,* are common causes of CAP especially in the outpatient setting either as primary pathogen or as a co-pathogen. Legionella is a cause of severe

 ISSN 1120-009X

TABLE 1 - *Microbiologic etiology of community-acquired pneumonia (CAP): formulating a differential diagnosis.*

Risk Factor	**Associated Etiologic Pathogens**
Alcoholism	*S. pneumoniae* including DRSP, oral anaerobes, *M. tuberculosis*
Chronic obstructive lung disease (COPD)	*S. pneumoniae, H. influenzae, M. catarrhalis, Legionella* species
Post-influenza	*S. pneumoniae, S. aureus, S. pyogenes, H. influenza, CA-MRSA*
Aspiration	Mixed aerobic/anaerobic/polymicrobial
Structural lung disease	*Pseudomonas* sp., *S. aureus*
Post obstructive CAP	Anaerobes, *S. pneumoniae, H. influenzae, S. aureus*
Exposure to mass gatherings: Hajj or Umrah	*Consider M. tuberculosis*
Exposure to cohorts, daycare centers, recent exposure to β-lactam therapy including in a family member, immunosuppression	DRSP

DRSP: Drug-resistant *S. pneumoniae*; CA-MRSA: community-acquired methicillin-resistant *S. aureus.*

CAP especially in patients with underlying immunosupression (*Table 1*). Although influenza remains the predominant viral cause of CAP in adults, other commonly recognized viruses include respiratory syncytial virus (RSV), adenovirus, and parainfluenza virus. In a recent study of immunocompetent adult patients admitted to the hospital with CAP, 18% had evidence of a viral etiology, and, in 9%, a respiratory virus was the only pathogen identified. Studies that include outpatients found viral pneumonia rates as high as 36%.

Antibiotic resistance is another major consideration in choosing empirical therapy. Resistance patterns vary by geography probably because of local antibiotic prescribing patterns or spread of resistant strains. Antibiotic resistance is probably more prevalent in developing than in developed nations [8] because of the availability of antibiotics over-the-counter. The emergence of drug-resistant pneumococcal isolates is well documented, but its clinical relevance is uncertain. A recent systematic review demonstrated that penicillin resistance is associated with higher mortality rates when compared to penicillin-susceptible strains in hospitalized patients with pneumococcal pneumonia [9].

Clinicians tend to consider national resistance patterns rather than patterns specific to local institutions [10]. Sergeti *et al* noted that though 70% of all nosocomial pathogens in the United States have developed resistance to at least one antimicrobial agent, clinicians still fail to recognize the extent of the problem in their own facilities [11]. There is no reason to assume these findings will be any different in the GCC region. Clearly, education regarding resistance rates and their impact on choice of agent is lacking, even in the most advanced healthcare settings.

LOCAL PERSPECTIVE

Common pathogens

While most data on microbiology of CAP is extrapolated from international work, some important local surveillance work sheds light on this important topic. Common pathogens include *S. pneumoniae, H. influenzae* and *M. catarrhalis* [12] (*Table 2*). In addition, several investigators document the importance of atypical pathogens including *M. pneumoniae*, *C. pneumoniae and Legionella pneumophila* in the etiology of CAP in the GCC region [13]. Note, even with the best techniques and early assessment, 30-60% of all cases of CAP do not yield positive microbiology. Recent data suggest that atypical organisms, such as *C. pneumoniae*, may serve as important co-pathogens with more 'typical' pathogens such as *S. pneumoniae*.

The agents causing CAP have been assessed in 112 adult patients admitted to the Armed Forces Hospital in Riyadh [14] during a one year period. Pathogens were identified in 78 patients (69.6%). *S. pneumoniae* was the commonest infecting agent (21.4%). Pneumonia due to *Mycobacterium tuberculosis* was diagnosed in eight patients (10.25%), that due to *M. pneumoniae* in seven (8.9%), to *Chlamydophila psittaci in* two (2.5%) and to *L. pneumophila* in one (1.2%). Three renal transplant patients had pneumonia caused by *S. aureus*, Cytomegalovirus and *Pneumocystis jirovecii* respectively, the latter diagnosed by lung biopsy. Two patients with acute *Brucella melitensis* infections developed pneumonia. In 34 patients (30.4%) the causative organism was never identified.

In another study from Saudi Arabia, a total of 567 pneumonic episodes in adult patients were reviewed retrospectively. An etiological diagnosis

TABLE 2 - *Local patterns of etiological pathogens: atypicals are common causes of community-acquired pneumonia (CAP) in the Gulf Corporation Council (GCC) Region.*

GCC Member State (n=pneumonic episode)	**Etiologic Diagnosis (most common to least common)**
Saudi Arabia (Riyadh, Armed Forces Hospital) (n=112)[14]	*S. pneumoniae, M. tuberculosis, M. pneumoniae*, *C. psittaci, S. aureus,* cytomegalovirus, *P. jirovecii*, *B. melitensis*
Saudi Arabia (other) (n=567) [15]	*S. pneumoniae, M. pneumoniae*
Saudi Arabia (Makkah at Hajj) (n=64)[16]	*M. tuberculosis*
Kuwait (n=124) [17]	*M. pneumoniae, L. pneumophila, C. pneumoniae,* Influenza B virus, Influenza A virus, *H. influenzae, S. pneumoniae, S. aureus,* enteric Gram-negative bacilli, *M. catarrhalis*
Oman (case report and serosurvey)[32-33]	*C. burnetii* (Q Fever)
Yemen (n=405)[18]	*M. pneumoniae*

was established in 351 (62%) cases, with 145 episodes due to pneumococcal infection and 129 to *Mycoplasma pneumoniae* [15]. Another study examined the pathogens of CAP during the 1994 Hajj [16]. Data was collected from patients admitted to Al-Noor Specialist Hospital and King Abdul Aziz hospital in Makkah between 3-28th May 1994. Bacteriological diagnosis was confirmed in 72% of patients (n=46*). M. tuberculosis* was the most common pathogen recovered among this hospitalized CAP population (20%).

In another study from Kuwait [17] examining 124 CAP admissions, etiological agents were identified from 44 patients (35%), with one causative pathogen identified in 31 patients (25%), two organisms found in 9 patients (7%), and three or more etiologic pathogens documented in 4 (3%) patients. The most common pathogens identified in this study were: *M. pneumoniae* in 14 patients (11%), *L. pneumophila* in 10 patients (8%), *C. pneumoniae* in 8 patients (6%), influenza B virus in 8 patients (6%), influenza A virus in 5 patients (4%), *H. influenzae* in 4 patients (3%), *S. pneumoniae* in 3 patients (2%), *S. aureus* in 3 patients (2%), enteric Gram-negative bacilli in 5 patients (4%), *M. catarrhalis* in 2 patients (2%), and viruses in 4 patients (3%).

In a study from Yemen [18], 405 patients with lower respiratory tract infections aged 10-60 years were tested for *M. pneumoniae* by 3 different methods: culture, antigen detection and IgM serology. There were 125 patients (30.9%) with current infection, mostly among younger age groups. These studies, along with other regional data [19-21], emphasize the importance of atypical pathogens in the etiology of CAP.

Other pathogens

Methicillin-resistant *S. aureus (*MRSA) is now increasingly recognized as a cause of community-acquired infection [2-7,22]. A 37-year-old Saudi male with no significant medical history was admitted with fever, respiratory distress and scrotal ulceration. Scrotal swabs and blood cultures grew MRSA. Imaging studies showed necrotizing pneumonia. There was no evidence of endocarditis. The patient was treated successfully with 4 weeks of intravenous vancomycin. The infection appears to have originated in the skin and subcutaneous tissues of the scrotum, and subsequently led to necrotizing pneumonia [22].

Increasingly, viral etiologies, particularly varicella zoster virus (VZV), have been recognized as causative pathogens of CAP within the region. Influenza will be considered in a separate discussion shortly. VZV CAP, however, has been specifically noted to be on the rise in the Kingdom of Saudi Arabia [23-30]. Non-immune adults including pregnant women are at increased risk for VZV pneumonia. Respiratory tract viruses are increasingly recognized causes of CAP. These infections are particularly serious in those with impaired immunity, namely the elderly, the very young and the immunosuppressed. Patients with other co-morbidities and structural lung disease are also at risk. The clinical presentation of viral CAP will depend on the host defenses of the patient and is frequently indistinguishable from bacterial CAP. Many patients admitted with documented bacterial CAP will have concomitant viral infections [31]. In this context a streptococcal or staphylococcal CAP may well represent a post viral superinfection.

Q fever was documented in Oman in two

patients, one with chronic pericarditis and the other with acute pneumonia [32,33]. In a randomly selected group of 102 adult patients, 10 (9.8%) were seropositive for previous *Coxiella burnetii* infection [33]. In a serology study on 75 military blood donors from Saudi Arabia, 30% tested positive for Q fever suggesting that this pathogen may be important in this area with large numbers of sheep [34].

In two observational studies from Saudi Arabia (one of which was conducted on CAP patients during Hajj [16]), *Mycobacterium tuberculosis* was among the commonest etiologic pathogens of CAP. If validated in other studies, this finding may have profound implications on the diagnostic approach, empiric therapy and infection control of CAP especially during Hajj.

ANTIBIOTIC RESISTANCE

Pneumococcal antibiotic resistance

Rates of antimicrobial resistance of *S. pneumoniae* are rising in the developing world, including the GCC region [35]. Pneumococcal susceptibility patterns have been studied in Saudi Arabia since 1982 at which time there was 100% sensitivity to penicillin [36]. Further surveillance showed no fully resistant strains, but reported a new finding of 10% prevalence of intermediately resistant strains to penicillin (minimum inhibitory concentration (MIC) 0.1-1 µg/ml) [37]. Within a year, in 1983, Chowdhury reported the first patient with a penicillin resistant strain of *S. pneumoniae* in Saudi Arabia [38]. Drug-resistant *S. pneumoniae* (DRSP) has since continued to increase in Saudi Arabia. Where once it was case reportable, now DRSP has become a common differential diagnosis and an all too familiar clinical challenge, just as in many other parts of the world. Current data show almost 60% of strains to have some degree of penicillin resistance [39]. DRSP-related CAP is associated with more suppurative complications of CAP than non resistant strains, is more likely to have a longer clinical course, but does not independently add to increased mortality overall. Identifying patients at risk of DRSP CAP is very important in anticipating the patient's likely clinical course. Of note, suppurative complications of the pleural space are particularly more often seen in the DRSP CAP patient and are more likely to be seen in the GCC region in the future.

Kambal and Abdullah in 1997 [40] described 49 children with pneumococcal bacteremia during a 5-year period at King Khalid University Hospital, Riyadh, Saudi Arabia. The majority (61.2%) were under 2 years of age. The focus of infection was either pneumonia, pharyngitis or undetermined in 28.6%, 18.4% and 20.4%, respectively. Antimicrobial susceptibility testing showed 20.4% of the isolates to be relatively penicillin-resistant. Resistance to other antimicrobial agents was also recorded with multiple resistance noted in 22% of isolates [40]. More recent surveillance data from the region echo these findings. Al-Swailem *et al* identified clones of invasive penicillin resistant pneumoccocus among isolates from Saudi patients [41]. The study period spanned October 2001 to July 2002 during which time bacterial isolates were collected from blood and cerebrospinal fluid (CSF) specimens from patients with either community acquired or nosocomial infection. All specimens were collected from laboratories in Riyadh. Susceptibility testing and serotyping were determined on the clinical isolates. Finally genotyping was performed using DNA extraction and amplification to identify resistance genes. In total, 296 isolates collected, 30.1% were invasive (84.3% from blood and 15.7% from CSF). Of these invasive strains, 19.1% were penicillin resistant. Most (88.2%) of these penicillin resistant strains were highly resistant to penicillin.

Memish *et al* examined the current prevalence of antibiotic resistance of *S. pneumoniae* isolates in the Kingdom of Saudi Arabia. During a 12-month study period from January to December of 2000, three major hospitals situated in each of the Kingdom's provinces provided *S. pneumoniae* isolates related to clinical illness. Multidrug resistance was highest in those aged 20-29 and those over 60 years of age. Both multidrug and penicillin resistance was most often noted in isolates from blood or cerebrospinal fluid, indicating that more invasive disease was associated with multidrug resistant strains. Ninety-one isolates (59%) were either intermediately or highly resistant to penicillin and 24 (15.6%) were multidrug resistant, with the lowest incidence of multidrug resistance being in the Central Province. Inpatient isolates were found to have a higher incidence of multidrug resistance compared to outpatients. Full resistance to penicillin was found in 14.9% of isolates. Tawfiq reported on the pattern of antibiotic resistance of *S. pneumoniae* in an Eastern Province hospital of Saudi Arabia [42]. Tawfiq identified isolates between January 1999 and December 2002. One hundred and sixty two isolates from both inpatients and outpatients were collated. Of these, 48.8% were penicillin non-susceptible. Overall 19.8% of all isolates showed high level resistance. No isolate was resistant to vancomycin but 12% of all isolates showed multidrug (greater than three-drug) resistance.

Similar findings are observed in other GCC countries. Surveillance data from Qatar conducted over a one month period from May to June 2003 examined clinical isolates from those with CAP [43]. Two hundred isolates were collected including *S. pneumoniae, H. influenzae* and *M. catarrhalis*. Of the 73 strains of pneumoccocus collected, 32% were penicillin resistant.

In a study from Kuwait, 53.8% of *S. pneumoniae* were penicillin-resistant [44]. This was confirmed by

another study which showed 46% of *S. pneumoniae* isolates to exhibit intermediate resistance and 9% full resistance to penicillin [45]. In another study also from Kuwait, full and intermediate resistance to penicillin was observed in 1.6% and 52.8% of the isolates respectively [46].

S. pneumoniae resistant to macrolide (erythromycin) accounted for 18.8% of isolates in a study from Saudi Arabia, most of which were of low-level resistance (M phenotype) (91%) [47]. In another study of 336 isolates *S. pneumoniae*, overall macrolide resistance rates were 22.6% to erythromycin, 18.5% to roxithromycin, 17.9% to azithromycin and 17.3% to clarithromycin [48]. Nevertheless newer macrolides, including azithromycin, remain drugs of choice for empiric treatment of respiratory infection in such circumstances. Macrolide resistance in Saudi Arabia is due to an efflux mechanism, and not a ribosomal mechanism, with the efflux mechanism being associated with substantially lower MIC values than the ribosomal mechanism [49]. Studies from Kuwait showed 40% pneumococcal resistance to TMP/SMX [45, 46].

Antibiotic resistance among other CAP pathogens

A number of investigators have examined antibiotic resistance in non-pneumococcal pathogens of CAP. Abdel-Rahman *et al* [50] conducted a point prevalence study examining resistance among *H. influenzae* isolates across the Kingdom of Saudi Arabia. Isolates of *H. influenzae* were collected in those diagnosed with an acute respiratory tract infection. A total of 129 specimens were obtained, the majority (85.3%) were retrieved from outpatients; 13.2% were resistant to ampicillin, 7% to tetracycline and 5.4% to chloramphenicol. Of all isolates, 5.4% exhibited multi-resistance, being resistant to all three agents. From this regional data, if *H. influenzae* is suggested as an etiologic pathogen, agents other than ampicillin should be considered. A study from Qatar found 35% of *H. influenzae* isolates to be β-lactamase producers and similarly almost all Moraxella isolated was positive for β-lactamase, indicating resistance to standard therapies [43]. In study of 116 *H. influenzae* isolates from Saudi Arabia, all were susceptible to all respiratory quinolones, except for trovafloxacin (99.1%) [47].

Studies examining *M. catarrhalis* in the GCC indicated >90% of isolates are β-lactamase producers [43, 47, 51, 52].

Within the Kingdom of Saudi Arabia, 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. In the study from Yemen, *M. pneumoniae* isolates were susceptible to all antibiotics in the in vitro antibiogram, with erythromycin being the most active [18].

RELATION OF ANTIBIOTIC RESISTANCE TO USAGE PATTERNS

Despite local regulations stipulating prescriptions prior to selling antibiotics, oral antibiotics are freely available over the counter in most GCC states. The market cost of drugs in the Kingdom of Saudi Arabia, for example, is determined by a centrally controlled committee at the Saudi Ministry of Health (MOH). These prices are based on wide analyses of manufacturers' prices from well over 40 countries. The MOH makes the most cost effective choice and hence many drugs are available at low cost. Most medications are not covered by health insurance or prescription plans 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 reality, the affordability of these drugs opens the gates to antibiotic abuse, by patient and practitioners alike.

The Saudi MOH stipulates that antibiotic availability for patients can only be authorized with a physician prescription. Unfortunately, this regulation is often violated and has thus far eluded enforcement. Antibiotics are widely available and dispensed into the community often without the recommendation of a clinician. This practice adds more antibiotic selection pressure to the environment, fueling resistance. This practice is mimicked throughout the GCC region except in Kuwait where stricter antibiotic dispensing is practiced.

In one study from Saudi Arabia, antibiotics were prescribed for most upper respiratory tract infections (83%) even though much of the pathogenic etiology is considered to be viral [53]. Similarly in a separate study in the Kingdom of Saudi Arabia, over 72% of prescribed antibiotics were considered misused [54]. Both observations indicate a pressing need for guideline development and implementation.

RECOMMENDATIONS

The GGC CAPWG considers the following to be the most common pathogens for CAP: *S. pneumoniae, H. influenzae* and *M. catarrhalis* (Level II evidence). Atypical pathogens such as *M. pneumoniae*, *C. pneumoniae* and *L. pneumophila* should also be considered in the etiology of CAP in the GCC region (Level II evidence).

Considering that TB remains highly prevalent in the GCC region, any patient presenting with CAP could potentially be a case of primary pulmonary TB. Appropriate diagnostic tests for *M. tuberculosis* should be considered in the proper setting if the patient presents with subacute or chronic symptoms

and fails to respond to the standard therapy for bacterial CAP. (Level II evidence).

Other less commonly encountered pathogens should be considered in patients with atypical presentations or unresolving pneumonia. These uncommon presentations include viral pathogens (such as influenza and varicella zoster viruses), MRSA or Q fever. (Level III evidence).

The GCC CAPWG notes that DRSP is on the rise in the GCC region (Level II evidence) and recommends that physicians be familiar with local prevailing antimicrobial resistance patterns both in the patient's community and the admitting institution. Physicians are encouraged to enquire about recent antibiotic history prior to presentation when considering likelihood of resistant pathogens from the outset is key. (Level III evidence).

The GCC CAP working group recommends that CAP bacteriology and resistance patterns be monitored (Level III evidence). The group also recommends that related governmental agencies put in place regulations to limit antibiotic prescription to physicians (Level III evidence). Multidisciplinary antimicrobial management teams are recommended to control antimicrobial resistance in hospitals (Level III evidence) [55].

FUTURE DATA AND VALIDATION

Multiple areas are in need of intense study and documentation. In the area of local microbiology, more detailed and representative studies are required. This can be achieved, for example, through multicenter surveillance for CAP etiology where screening for atypical and less common pathogens could be systematically applied. In addition to the common bacteria isolated in routine cultures, specific testing for *Mycoplasma* spp., *Chlamydophila* spp., *Legionella* spp., Q fever and respiratory virus needs to be documented. Serologic testing is currently underutilized in the diagnosis of CAP and efforts should be made to make these tests readily available for physicians treating CAP patients. The true regional prevalence of tuberculosis, specifically in CAP patients as well as within the wider population at risk also warrants careful study. Antimicrobial resistance should be monitored among common pathogens in the GCC region as well as the impact of this resistance on morbidity and mortality. Finally, there is a need for more studies on the relationship between local antibiotic use patterns and bacteriological resistance in the GCC region.

REFERENCES

[1] Arabi Y, Gomersall C, Ahmed Q, Boynton B, Memish Z. The critically ill avian Influenza A (H5N1) Patient. Crit Care Med 2007; 35(5): 1397-1403.

[2] Drews TD, Temte JL, Fox BC. Community-associated methicillin-resistant Staphylococcus aureus: review of an emerging public health concern. Wmj 2006; 105(1): 52-7.

[3] Pfaller MA, Jones RN. Gatifloxacin phase IV surveillance trial (TeqCES study) utilizing 5000 primary care physician practices: report of pathogens isolated and susceptibility patterns in community-acquired respiratory tract infections. Diagn Microbiol Infect Dis 2002; 44(1): 77-84.

[4] Enayet I, Nazeri A, Johnson LB, Riederer K, Pawlak J, Saravolatz LD. Community-associated methicillin-resistant *Staphylococcus aureus* causing chronic pneumonia. Clin Infect Dis 2006; 42(7): e57-60.

[5] Levison ME, Fung S. Community-associated methicillin-resistant *Staphylococcus aureus:* reconsideration of therapeutic options. Curr Infect Dis Rep 2006; 8(1): 23-30.

[6] Frazee BW, Salz TO, Lambert L, Perdreau-Remington F. Fatal community-associated methicillin-resistant *Staphylococcus aureus* pneumonia in an immunocompetent young adult. Ann Emerg Med 2005; 46(5): 401-4.

[7] Slama TG, Amin A, Brunton SA, File TM, Jr., Milkovich G, Rodvold KA, et al. A clinician's guide to the appropriate and accurate use of antibiotics: the Council for Appropriate and Rational Antibiotic Therapy (CARAT) criteria. Am J Med 2005; 118 Suppl 7A: 1S-6S.

[8] Qadri SM, Ostrawski S, Johnson S, Flournoy DJ. Differences in antimicrobial susceptibilities of clinical isolates in Saudi Arabia and the United States. J Natl Med Assoc 1987; 79(4): 433-7.

[9] Tleyjeh IM, Tlaygeh HM, Hejal R, Montori VM, Baddour LM. The impact of penicillin resistance on short-term mortality in hospitalized adults with pneumococcal pneumonia: a systematic review and meta-analysis. Clin Infect Dis 2006; 42(6): 788-97.

[10] Giblin TB, Sinkowitz-Cochran RL, Harris PL, Jacobs S, Liberatore K, Palfreyman MA, et al. Clinicians' perceptions of the problem of antimicrobial resistance in health care facilities. Arch Intern Med 2004; 164(15): 1662-8.

[11] Segreti J, House HR, Siegel RE. Principles of antibiotic treatment of community-acquired pneumonia in the outpatient setting. Am J Med 2005; 118 Suppl 7A: 21S-28S.

[12]. Ewig S. Community-acquired pneumonia: definition, epidemiology, and outcome. Semin Respir Infect 1999; 14(2): 94-102.

[13] Reimann HA. Landmark article Dec 24,1938: An acute infection of the respiratory tract with atypical pneumonia. A disease entity probably caused by a filtrable virus. By Hobart A. Reimann. Jama 1984; 251(7): 936-44.

[14] Mohamed AR, Evans DA. The spectrum of pneumonia in 1983 at the Riyadh Armed Forces Hospital. J Infect 1987; 14(1): 31-7.

[15] Kurashi NY, Al-Hamdan A, Ibrahim EM, Al-Idrissi HY, al-Bayari TH. Community acquired acute bacterial and atypical pneumonia in Saudi Arabia. Thorax 1992; 47(2): 115-8.

[16] Alzeer A, Mashlah A, Fakim N, Al-Sugair N, Al-Hedaithy M, Al-Majed S, et al. Tuberculosis is the commonest cause of pneumonia requiring hospitalization during Hajj (pilgrimage to Makkah). J Infect 1998; 36(3): 303-6.

[17] Behbehani N, Mahmood A, Mokaddas EM, Bittar Z, Jayakrishnan B, Khadadah M, et al. Significance of atypical pathogens among community-acquired pneumonia adult patients admitted to hospital in Kuwait. Med Princ Pract 2005; 14(4): 235-40.

[18] Al-Moyed KA, Al-Shamahy HA. Mycoplasma pneumoniae infection in Yemen: incidence, presentation and antibiotic susceptibility. East Mediterr Health J 2003; 9(3): 279-90.

[19] Somer A, Salman N, Yalcin I, Agacfidan A. Role of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in children with community-acquired pneumonia in Istanbul, Turkey. J Trop Pediatr 2006; 52(3): 173-8.

[20] Lieberman D, Schlaeffer F, Lieberman D, Horowitz S, Horovitz O, Porath A. *Mycoplasma pneumoniae* community-acquired pneumonia: a review of 101 hospitalized adult

patients. Respiration 1996; 63(5): 261-6.

[21] Lieberman D, Lieberman D. Community-acquired pneumonia in the elderly: a practical guide to treatment. Drugs Aging 2000; 17(2): 93-105.

[22] Al-Tawfiq JA, Aldaabil RA. Community-acquired MRSA bacteremic necrotizing pneumonia in a patient with scrotal ulceration. J Infect 2005; 51(4): e241-3.

[23] Adhami N, Arabi Y, Raees A, Al-Shimemeri A, Ur-Rahman M, Memish ZA. Effect of corticosteroids on adult varicella pneumonia: cohort study and literature review. Respirology 2006; 11(4): 437-41.

[24] Abba AA, Al-Khuwaitir TS, Al-Moghairi AM, Garg H. Presentation and outcome of varicella pneumonia in adults. Saudi Med J 2005; 26(2): 338-40.

[25] Ahmed R, Ahmed QA, Adhami NA, Memish ZA. Varicella pneumonia: another 'steroid responsive' pneumonia? J Chemother 2002; 14(2): 220-2.

[26] Almuneef M, Dillon J, Abbas MF, Memish Z. Varicella zoster virus immunity in multinational health care workers of a Saudi Arabian hospital. Am J Infect Control 2003; 31(6): 375-81.

[27] Almuneef M, Memish ZA, Abbas ME, Balkhy HH. Screening healthcare workers for varicella-zoster virus: can we trust the history? Infect Control Hosp Epidemiol 2004; 25(7): 595-8.

[28] Almuneef M, Memish ZA, Balkhy HH, Alotaibi B, Helmy M. Chickenpox complications in Saudi Arabia: Is it time for routine varicella vaccination? Int J Infect Dis 2006; 10(2): 156-61.

[29] Almuneef MA, Memish ZA, Balkhy HH, Otaibi B, Helmi M. Seroprevalence survey of varicella, measles, rubella, and hepatitis A and B viruses in a multinational healthcare workforce in Saudi Arabia. Infect Control Hosp Epidemiol 2006; 27(11): 1178-83.

[30] Memish ZA, Oni GA, Bannatyne RM, Qasem L. The cost-saving potential of prevaccination antibody tests when implementing a mass immunization program. Mil Med 2001; 166(1): 11-3.

[31] Mandell LA, Bartlett JG, Dowell SF, File TM, Jr., Musher DM, Whitney C. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis 2003; 37(11): 1405-33.

[32] Scrimgeour EM, Johnston WJ, Al Dhahry SH, El-Khatim HS, John V, Musa M. First report of Q fever in Oman. Emerg Infect Dis 2000; 6(1): 74-6.

[33] Scrimgeour EM, Al-Ismaily SI, Rolain JM, Al-Dhahry SH, El-Khatim HS, Raoult D. Q Fever in human and livestock populations in Oman. Ann N Y Acad Sci 2003; 990: 221-5.

[34] Bannatyne RM, Qasem L. Aetiology of community acquired pneumonia: fashionable or familiar. Saudi Med J 2000; 21(1): 104.

[35] Memish ZA, Balkhy HH, Shibl AM, Barrozo CP, Gray GC. *Streptococcus pneumoniae* in Saudi Arabia: antibiotic resistance and serotypes of recent clinical isolates. Int J Antimicrob Agents 2004; 23(1): 32-8.

[36] Mahgoub E, Hussein S. *Streptococcus pneumoniae* serotypes and their minimal inhibitory concentrations to penicillin in Riyadh. Saudi Med Journal 1986; 7: 149-54.

[37] Shibl A, Hussain S, Bahakime H, Sofan M. Activity of penicillin imipenem and teicoplanin against various *Streptococcus pneumoniae* serotypes isolated in Riyadh. In Berkarda B, Kuemmerle HP, editors. Proceedings of the 15th International Congress of Chemotherapy - Progress in Antimicrobial and Anticancer Chemotherapy, Antimicrobial Section I. Istanbul 1987: 757-9.

[38] Chowdhury MN. A penicillin-resistant *Streptococcus pneumoniae*; case report. Trop Geogr Med 1983; 35(3): 309-11.

[39] Memish Z, Osoba A, Shibl A, Mokaddas E, Venkatesh S, Rotimi VO. Emergence and trends of penicillin non-susceptible *Streptococcus pneumoniae* in Saudi Arabia and Kuwait - Perspective and Outstanding Issues. J Chemother. 2007; 19(5): 471-480.

[40] Kambal AM, Abdullah AM. Childhood pneumococcal bacteraemia in Riyadh, Saudi Arabia. Ann Trop Paediatr 1997; 17(3): 245-51.

[41] Al-Swailem A, Kadry A, Fouda S, Shibl A, Shair O. Phenotypic and Genotypic Characterization of Invasive Streptococcus pneumoniae Clinical Isolates. Current Therapeutic Research 2004; 65(5): 423-432.

[42] Al-Tawfiq JA. Pattern of antibiotic resistance of *Streptococcus pneumoniae* in a hospital in the Eastern Province of Saudi Arabia. J Chemother 2004; 16(3): 259-63.

[43] Elshafie SS, Al-Kuwari J. In vitro activity of moxifloxacin against community respiratory pathogens in Qatar. Int J Antimicrob Agents 2004; 24(3): 309-10.

[44] Ahmed K, Wilson S, Jamal WY, Martinez G, Oishi K, Nagatake T, et al. Causative bacteria of respiratory tract infections in Kuwait by quantitative culture of sputum. J Infect Chemother 1999; 5(4): 217-219.

[45] Ahmed K, Martinez G, Wilson S, Yoshida R, Dhar R, Mokaddas E, et al. The prevalence and clonal diversity of penicillin-resistant *Streptococcus pneumoniae* in Kuwait. Epidemiol Infect 2000; 125(3): 573-81.

[46] Mokaddas EM, Wilson S, Sanyal SC. Prevalence of penicillin-resistant *Streptococcus pneumoniae* in Kuwait. J Chemother 2001; 13(2): 154-60.

[47] Balkhy HH, Memish ZA, Shibl A, Elbashier A, Osoba A. In vitro activity of quinolones against *S. pneumoniae, H. influenzae* and *M. catarrhalis* in Saudi Arabia. East Mediterr Health J 2005; 11(1-2): 36-44.

[48] Fouda SI, Kadry AA, Shibl AM. Beta-lactam and macrolide resistance and serotype distribution among *Streptococcus pneumoniae* isolates from Saudi Arabia. J Chemother 2004; 16(6): 517-23.

[49] Shibl AM. Patterns of macrolide resistance determinants among *S. pyogenes* and *S. pneumoniae* isolates in Saudi Arabia. J Int Med Res 2005; 33(3): 349-55.

[50] Abdel-Rahman EM, Ismael NA, Dixon RA. Antibiotic resistance and prevalence of beta-lactamase in *Haemophilus influenzae* isolates-a surveillance study of patients with respiratory infection in Saudi Arabia. Diagn Microbiol Infect Dis 2000; 36(3): 203-8.

[51] Babay HA. Isolation of *Moraxella catarrhalis* in patients at King Khalid University Hospital, Riyadh. Saudi Med J 2000; 21(9): 860-3.

[52] Kadry AA, Fouda SI, Elkhizzi NA, Shibl AM. Correlation between susceptibility and BRO type enzyme of *Moraxella catarrhalis* strains. Int J Antimicrob Agents 2003; 22(5): 532-6.

[53] el-Gilany AH. Acute respiratory infections in primary health care centres in northern Saudi Arabia. East Mediterr Health J 2000; 6(5-6): 955-60.

[54] Al-Ghamdi S, Gedebou M, Bilal NE. Nosocomial infections and misuse of antibiotics in a provincial community hospital, Saudi Arabia. J Hosp Infect 2002; 50(2): 115-21.

[55] Struelens MJ. Multidisciplinary antimicrobial management teams: the way forward to control antimicrobial resistance in hospitals. Curr Opin Infect Dis 2003; 16(4): 305-7.

REPRINT

Journal of Chemotherapy Vol. 19 - Supplement n. 1 (25-31) - 2007

Clinical Presentation and Diagnostic Workup for Community-Acquired Pneumonia: The Gulf Corporation Council CAP Working Group Consensus Statement

Z.A. MEMISH [1] - Y.M. ARABI [2] - Q.A. AHMED [3] - H. AL JAHDALI [4] - A.M. SHIBL [5] M.S. NIEDERMAN [6] AND THE GCC CAP WORKING GROUP (GCC-CAPWG)

Departments of [1] Infection Prevention and Control, [2] Intensive Care Medicine, 4Internal medicine, King Abdulaziz Medical City, Riyadh, Saudi Arabia, [3] Department of Medicine, Medical University of South Carolina, Charleston, South Carolina, USA, [5] Department of Microbiology, King Saud University Hospital, Riyadh, Saudi Arabia, [6] Department of Medicine, Winthrop-University Hospital, New York, USA

Corresponding author: Ziad A. Memish MD, FACP, FRCPC, FIDSA, Executive Director, Infection Prevention and Control, National Guard Health Affairs and Director, GCC Center for Infection Control, King Abdulaziz Medical City, Riyadh, P.O. Box 22490, Riyadh 11426, Kingdom of Saudi Arabia and Adjunct Professor of Medicine, University of Ottawa, Ottawa, Canada. Tel. No.: +966-1-2520088 x 43718; Fax No.: +966-1-2520437.
E-mail: zmemish@yahoo.com, memish@ngha.med.sa

Summary

Community-acquired pneumonia (CAP) is diagnosed on the basis of a suggestive history and 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. With the rise in elderly Gulf Cooperation Council (GCC) residents, CAP is likely to present with non-classical manifestations such as somnolence, new anorexia, and confusion and carries a worse outcome than CAP in their younger counterparts. Tuberculosis should be considered in the differential diagnosis of unresolving CAP in the GCC region. Diagnostic work up depends on severity of CAP, clinical course and underlying risk factors.

Key words: **Community-acquired pneumonia, diagnosis, CAP.**

CLINICAL PRESENTATION OF COMMUNITY-ACQUIRED PNEUMONIA (CAP)

INTERNATIONAL PERSPECTIVE

The clinical presentation of CAP varies according to the host incubating the infection, the stage at which the patient presents to medical attention and the infecting pathogen. Over recent years, the distinction between the clinical presentation of 'typical' (i.e. pneumoccoccal) and 'atypical' pneumonia has been deliberately down played since both presentations intermingle more often than not. What is perhaps better replicated is a classic presentation associated with the younger patient (under 65) in contrast to those over 65 who present in a more attenuated fashion.

The historical distinction of 'typical' from 'atypical' pneumonia first arose during the early and mid twentieth century in relation to *Mycoplasma pneumoniae,* which was found to have a distinct presentation from those infected with *Streptococcus pneumoniae* [1]. Such 'atypical' infection can be associated with extra-pulmonary manifestations. *M. pneumoniae* is often associated with pharyngitis, earache and a rash, asides from symptoms and signs indicative of a lower respiratory tract infection. *Legionella pneumophila* is well recognized to have multiple extra-pulmonary manifestations including diarrhea and abnormal liver function. However, it is important to note that clinical presentation in most instances cannot be reliably considered pathognomonic for either atypical or typical etiologic agents. The presentation

 ISSN 1120-009X

varies according to the virulence of the infecting agent and the presence of concomitant underlying conditions in the host.

New cough, shortness of breath, pleuritic pain, fever, purulent or newly altered sputum production and diaphoresis are all classic, 'typical' presenting symptoms of CAP. The severity of these symptoms varies according to the host's response to the inciting agent: a young patient with an intact immune system when adequately inoculated with a virulent organism will respond with an intense host immune response in an effort to contain and compartmentalize the infection. This response can be likely to produce focal symptoms including pain, pleuritic symptoms, parapneumonic effusion and fever.

In contrast, an older immuno-incompetent patient will not be able to mount such an intense response and consequently the presentation is 'blunted': elderly patients often present with somnolence, new anorexia, and confusion [2]. A study to evaluate the association between age and presenting symptoms in patients with CAP was performed by Metlay *et al*. In a review of 1812 patients with CAP, fewer patients reported symptoms as age advanced. Also the duration of many symptoms was found to be longer in older patients [2]. Riquelme *et al* studied 101 patients age 65 or older with hospitalized CAP. Most had comorbid illness including COPD, cardiac, neurologic comorbidities or underlying malignancy. The mean duration of symptoms was 6 days. Most (n=62) had a delay of more than 72 hours from onset to diagnosis. Half the time delay was due to the patient not reporting symptoms, the remainder delay was due to the attending clinician and patient's relatives. Awareness of CAP in these elderly patients was therefore limited in patients, social contacts and physicians. Often the symptoms were 'incomplete': 19 of the 101 had no cough, no sputum production or no pleuritic chest pain. The majority (78%) presented with malnutrition [3]. Nevertheless symptoms in the elderly with CAP do include cough, sputum, dyspnea, fatigue, anorexia, myalgia and even abdominal pain. Also, statistically significant reductions in symptom reporting was found in older patients even when documented etiologies of CAP (*S. pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus* and mixed infections) are established [2]. Cough, chest pain, dyspnea and fever are frequently absent in the older CAP patient [4,5]. Tachypnea, a physical sign oftentimes poorly recorded, is more common with older age and should always raise clinical suspicion of CAP in this age group [2] (*Table 1*).

Recognizing significant variations in presentation is key to making early presumptive diagnoses of CAP in the elderly who would otherwise present more often with later, more established and complex parenchymal infection [6-8]. Additionally, when the elderly patient develops CAP they tend to have a worse outcome than younger counterparts [9] .

Considering the pneumococcus, specific note must be made of drug resistant pneumococcus

TABLE 1 - *Clinical presentation of CAP varies according to patient age [2, 3].*

Adults Age <65	**Adults Age >65**
More symptoms	Fewer symptoms
Shorter symptom duration	Longer symptoms duration
Earlier reporting both by patient and recognition by physician	Delay is both due to patient or family AND clinician's failure to recognize
Cough, sputum production, pleuritic pain, dyspnea occur more often than in elderly	Cough, sputum production, pleuritic pain, dyspnea are less common
Classical presentation more common	Non classical presentation predominates: fatigue, anorexia, myalgia, abdominal pain
Fever is common	Fever is less common
Complications will present more overtly and allow earlier clinical diagnosis	Advanced complications of infection may be the presenting impetus: empyema, for instance, may present only with weight loss.
Tachypnea less common	Tachypnea more common
Malnutrition less common	Malnutrition very common
Clinical spectrum more complete	Incomplete clinical spectrum

(DRSP), which is known to more commonly suppurate, and therefore often present with empyemas or other infected, complicated pleural spaces. These pneumonias can be particularly aggressive, resulting in longer hospitalizations and more frequent Intensive Care Unit (ICU) admissions even in a young previously healthy patient [10].

Though no single presentation is definitive, any variation of the above in the appropriate host can be strongly suggestive of CAP. Even today, CAP remains a clinical diagnosis, which can only be supported by certain laboratory data. There remains a need to develop rapid, inexpensive, sensitive and specific tests for the diagnosis of respiratory infections. Some useful antigen tests are already widely available and can aide the initial diagnosis but all too often the diagnosis is at best a supposition.

LOCAL PERSPECTIVE

With the rise in elderly GCC residents across the GCC region, CAP in the elderly is likely to be more often encountered and will increase burden on the regional healthcare economy. This problem cannot be underestimated: the GCC population is graying, a phenomenon which masks the average demographic age because of high regional fertility and per capita birth rates. During the World Assembly on Ageing (2002) [11], several Middle East countries reported in on their current and projected populations over 60 years. At a national level, Egypt was found to have the highest number of people aged 60 years and older, at 4.3 million or 6.3% of the total population in 2000, which is set to rise to some 23.7 million or 20.8% by 2050. Within the context of absolute populations within the entire Middle East, that age bracket is projected to exceed 10 million in Algeria and Morocco, and 5 million in five other countries: Iraq, Saudi Arabia, Sudan, Syrian Arab Republic and Yemen. By 2050, approximately a quarter of the populations in five countries are expected to be aged 60 years and older: Bahrain, at 24.0%; Kuwait, at 25.7%; Lebanon, at 25.4%; Tunisia, at 24.6%; and United Arab Emirates, at 26.7%. There are significant regional disparities that can be attributed to the varying stages of demographic transition and, more specifically, to differences in fertility and mortality rates [11].

Mention must be made of the high prevalence of tuberculosis in the GCC region. Physicians should keep a high index of suspicion in patients who present with CAP which remains unresolving as tuberculosis may present as CAP in this part of the world. Tuberculosis should also be suspected in patients who present with subacute or chronic presentation, immunocompromized patients and patients who have history of contact with a patient with tuberculosis. The diagnostic work up and management of primary tuberculosis falls beyond the scope of this paper.

History taking should be comprehensive and include information that helps in directing towards certain pathogens or in risk stratification. This include recent contacts with individuals with respiratory tract symptoms, animal or bird contacts, recent performance of Hajj or Umra, travel history, antibiotic use, smoking and vaccination history, structural lung diseases and steroid use.

RECOMMENDATIONS

The distinction between the clinical presentation of 'typical' (i.e. pneumoccoccal) and 'atypical' pneumonia is imprecise. Clinicians should rather focus on other variables such as age and co-morbidities in directing empiric therapy (Level II evidence). CAP in older patients often manifests with non-classical presentations such as somnolence, new anorexia, and confusion and tends to have worse outcome (Level II evidence). CAP caused by DRSP is associated with more aggressive course and poor outcome (Level II evidence). Tuberculosis should be considered in the differential diagnosis of unresolving CAP in the GCC region (Level II evidence).

FUTURE DATA AND VALIDATION

Our review showed paucity of data on clinical presentation of CAP in the GCC region. The GCC CAP working group recommends data collection on clinical presentation and its relationship to bacteriology.

DIAGNOSTIC TOOLS

INTERNATIONAL PERSPECTIVE

Chest X-ray provides only supportive evidence of pulmonary infection and the optimal use of imaging in the diagnosis of pneumonia is to be determined. A radiological exam showing *new* airspace disease is currently prerequisite for the diagnosis of any pneumonia and integral to recognizing CAP. Knowledge of a pre-morbid film is essential in order to determine whether abnormalities seen are actually new for the patient in question. It is well recognized that emergency room physicians may 'over-read' radiology of the CAP patient in an effort to avoid 'missed diagnosis' of CAP and to avoid delay in treatment[12].

Aside from diagnosis, radiology also helps determine whether response to therapy is occurring, though radiological resolution always lags behind clinical presentation. Radiological resolution of CAP in a normal host lung occurs over 4-6 weeks following onset of CAP. Follow up films to assess resolution should not be ordered any earlier, unless clinical circumstances are worsening or films are indicated for other reasons. Those with structurally abnormal

lungs, aging lungs or other co-morbidities may be much slower in resolving on chest X-ray and these allowances are important to consider if one is to avoid the pitfall of treating the chest X-ray rather than the patient.

High resolution computerized tomography (HRCT) scanning is known to be more sensitive for detection of parenchymal air space disease in those admitted to hospital with CAP but the clinical significance of these findings is unclear [13]. CT scan is indicated for diagnosis of CAP complications or alternative diagnosis but not indicated as part of routine evaluation.

The utility of sputum gram stain and culture in CAP has been questioned. In managing CAP as an outpatient, sputum Gram stain is valuable only in CAP outpatients with suspected resistant pathogens or in patients who did not respond to initial therapy rather than as an initial 'sweep' for etiologic pathogens at the outset. Gram stain of sputum should probably not be used to narrow the spectrum of the antibiotic used in the initial treatment of CAP.

Routine blood cultures are not recommended for the evaluation of mild, outpatient CAP [14] and in fact there is even debate in the literature regarding limitation of 'reflex' culturing of the blood of all CAP patients. This is a response to evidence that culture positive data remain poor and that examination of clinical settings ranging from community general hospitals to academic teaching institutions all find poor overall identification rates [15]. In response, some suggest efforts to culture blood should be targeted to higher risk, more severely ill patients, namely those who are hospitalized. In these settings, bacteremia can dictate more severe disease, carrying mortality rates ranging from 6-20% [16].

A randomized controlled trial compared pathogen directed treatment (PDT) approach with an empirical broad spectrum antibiotic treatment (EAT) and found comparable clinical efficacy to both approaches [17].

Routine laboratory data in the outpatient setting are indicated if the likelihood of hospitalization seems high or if the assessment of disease severity (discussed shortly) appears high. Recommended laboratory data for assessment include complete blood count with differential to look for neutrophilia, electrolytes and possibly liver function tests.

An important part of the outpatient assessment of the CAP patient is pulse oximetry. This is advisable in all patients but particularly in those with underlying comorbidities including chronic or structural lung disease (such as bronchiactesis) or concomitant cardiac disease. Pulse oximetry is readily available, inexpensive and non invasive. The clinician can also be aided in disposition related decision-making, reassured that a patient relegated to oral antibiotics in the community is not hypoxemic. If hypoxemia is found, need for supplemental O2 can be an independent indicator for hospitalization - especially useful in assessing blunted presentations of elderly CAP patients presenting to the office or emergency room.

For the inpatient with CAP, aggressive diagnostic work-up in a timely fashion is essential. This will include chest radiology, sputum and most likely blood culture data, complete blood count, electrolytes, liver function and on occasion other data which may be impacted by future therapy - theophylline levels if relevant and coagulation parameters (if the patient is on warfarin). Oxygen saturation is assessed as outlined above but with a low threshold for arterial blood gas sampling if the patient has a significant O_2 requirement, is rapidly deteriorating, or is apparently in respiratory failure. Additionally, those with preexisting lung disease should have arterial blood gas sampling earlier rather than later in view of their added vulnerability for respiratory failure due to impaired cardiopulmonary reserve. Arterial blood gas data will aide appropriate in-hospital triage depending on the perceived/impending need for more invasive support.

When patients present with a parapneumonic effusion revealed by radiology, efforts should be made to sample the fluid if the effusion is of significant size or there is suspicion of complicated parapneumonic effusion. The ATS recommends sampling if more than 10 mm of fluid is visible on a plain lateral decubitus film [18]. Notice that antibiotics do not need to be withheld before sampling is completed (in fact thoracocentesis may be delayed while equipment is assembled, the patient is admitted and coagulopathies are ruled out) never the less pleural fluid analysis can be useful. Additionally, it is essential to exclude an empyema, which will need a combination of pleural space management, antimicrobials and possible surgical intervention.

Other rapidly processed tests are also now entering the diagnostic repository and clinicians are learning to use these with increasing familiarity. The urinary antigen test for Legionella can be used on admission and is positive in most patients with acute infection due to *Legionella pneumophila serogroup 1*. Unfortunately antigen is present in the urine for months after an infection so its utility is limited to those patients without a recent history of Legionella. This assay has been selected for a number of reasons, based on available alternatives and their practical implications. Legionella can be diagnosed via culture, serology, immune-assay or PCR methods. PCR methods on samples of sputum, serum, urine (or even contaminated water suspected to be implicated in an outbreak) are sensitive (33-70%) and highly specific (98-100%) [19]. Additionally PCR testing can be completed in 2-4 hours but the utility of this test is limited by prohibitive costs and lacks approved reagents. Direct fluorescent antibody testing of the sputum of a CAP patient suspected to have Legionella is also quickly processed in 2-4 hours with similar sensitivities and specificities.

Interpretation of DFA however takes significant expertise and requires a large pathogen burden, which can only be expected in those with multi-lobar pneumonia. Single point serology is useful only if baseline IgM or IgG is greater or equal to 1: 128 and acute and convalescent titers otherwise need to demonstrate a four-fold rise when compared several weeks apart - too late to have any impact on chosen therapy at the time of CAP presentation. Sputum culture, when using special media, remains the gold standard but it takes from 2 to 7 days before the final culture result can be read. The urinary antigen therefore emerges as the ideal test for the CAP patients who are immunocompetent because sensitivity and specificity are both between 90 and 100% and the test is processed in minutes to a couple of hours (depending on which method is used). Since most CAP infections are due to *L. pneumophila* serogroup 1 which is the only pathogen detected by the urinary antigen test (for instance *Legionella longbeacheae* is not detected) this does not present a significant limitation in clinical practice for most CAP patients. In fact the guidelines now endorse use of the urinary antigen test supplemented by a concurrent sputum culture as confirmatory evidence of Legionella CAP [16].

Pneumococcal antigen is a similar case in point offering newly recognized advantages. The IDSA advises its use in conjunction with standard culture data noting that it provides results potentially as quickly as a standard sputum gram stain [16]. An assay for pneumococcal antigen has been approved by the FDA using a urine sample and confirms the presence of pneumococcal infection by detecting pneumococcal cell wall polysaccharide, which is shared by all pneumococcal serotypes. The assay is an immunochromatographic membrane test (ICT). Significantly, sensitivity for detecting bacteremic pneumococcal infection is high, between 70-90%. Also a major advantage of this new assay is that the ICT for pneumococcal antigen detects disease in those who are culture negative. It may also be helpful for those patients presenting with CAP while on antibiotics prescribed earlier. The ICT will aid diagnostic evaluation rather than supplant culture data, because cultured data are still required in order to ascertain susceptibility to specific agents. It is important to note that the pneumococcal antigen will be positive in those infected with other agents but colonized with pneumococcus so a positive ICT for this antigen does not absolutely confirm active infection, merely suggest it [16].

Similarly, PCR assays for Mycoplasma on throat swab samples are also being examined and are helping secure a diagnosis in many CAP patients. DNA probes and nucleic acid amplification assays are under development but remain research tools at present.

Chlamydophila pneumoniae is also an important pathogen for CAP but lacks a gold standard diagnostic method. Serology, culture, microimmunofluorescence (MIF), PCR, tissue histology and immunohistochemistry are all possible options in establishing a diagnosis of *Mycoplasma pneumoniae* infection. For the CAP patient, detection of four fold increases in IgM antibody titers to *M. pneumoniae* measured by MIF are probably most useful but remain a research tool at the moment. Single elevated IgG titers should not be considered diagnostic because there is significant day-to-day variation in these levels - instead acute and convalescent samples should be studied.

Finally, invasive diagnostic tests may be appropriate but these will be reserved for the hospitalized 'enigmatic' pneumonia, which is progressing with high severity. Techniques include transtracheal aspiration, bronchoscopy with bronchoalveolar lavage and possibly protected specimen brush sampling. Finally trans-thoracic needle aspiration of the lung (limited to few experienced operators) may also be indicated. In rare instances, some patients who show signs of rapid deterioration or severe lung injury may ultimately need open lung biopsy.

Procalcitonin has been proposed as a diagnostic tool for CAP as well as in predicting severity, prognosis and in guiding therapy [20-29].

Other laboratory data may be of use in assessing the course of CAP or the response to therapy. An elevated C-reactive protein (CRP) on presentation is suggestive of an acute infective process. CRP has been correlated with clinical progress. [30] A simple algorithm follows listing the basic steps in diagnostic evaluation for the CAP patient recommended (*Figure 1*). Actual diagnostic work up may not follow this, either sequentially or exhaustively, because the diagnostic work up will also be dependent on clinical course and underlying risk factors, the focus of discussion in subsequent sections.

LOCAL PERSPECTIVE

The use of different tests of CAP in different areas of the GCC region depends on the availability and the cost of the tests. Diagnostic testing for CAP including microbiology, serology, and radiology in addition to basic laboratory workup is available in most areas of the GCC region. In tertiary care centers more sophisticated testing facilities are available including Legionella testing, Mycoplasma and Chlamydia serology, procalcitonin, HRCT, bronchoscopy and molecular testing. More comprehensive diagnostic testing is more likely to be done in governmental or teaching hospitals compared to private setting and in major tertiary care centers compared to primary and peripheral hospitals and clinics. However, there is limited data from the region on the utility of these tests in CAP management.

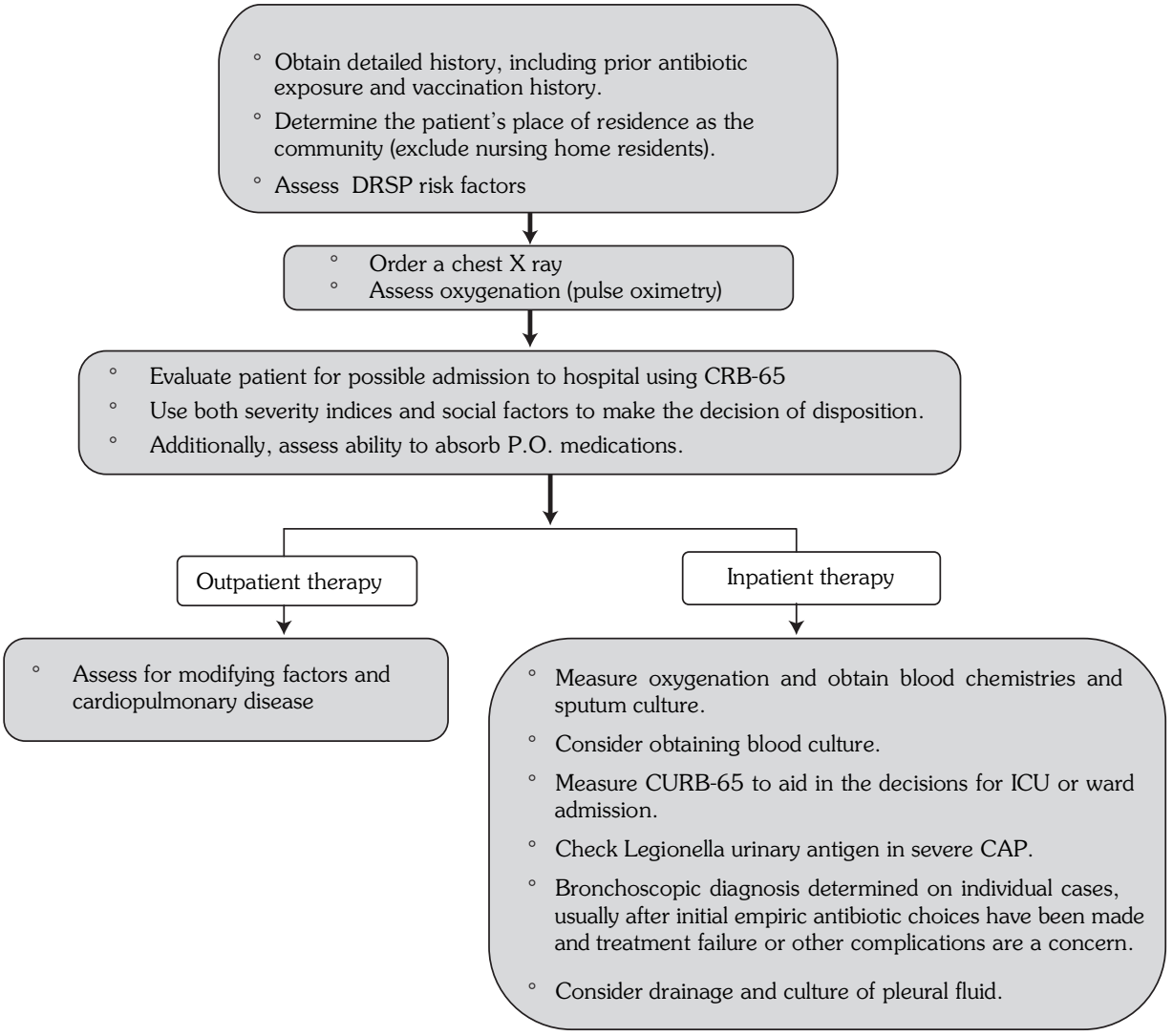

FIGURE 1 - Diagnostic algorithm for community acquired pneumonia patient: determination of disposition, severity and co-morbidities.

RECOMMENDATIONS

Chest radiograph is recommended for all patients with CAP to establish the diagnosis and the presence of complications (Level II evidence), even allowing for the difficulty in interpreting chest x-rays in milder disease or in the emergency rooms. Efforts to obtain an old CXR should always be made in order to make a comparison to determine new changes.

For outpatients with CAP, Gram stain and culture of sputum or blood are not required. Oxygen saturation should be assessed by pulse oximetry if available (Level II evidence).

For hospitalized patients, Gram stain and culture of sputum should be obtained if a drug-resistant or unusual pathogen is being considered (Level II evidence). Good-quality sampling is mandatory for informative results. Ideally all culture data, sputum or blood must be obtained prior to initiation of antibiotics. Assessment of gas exchange, routine blood chemistry and blood count should be performed (Level II evidence). For those with severe CAP, the following tests should also be obtained: blood cultures and urinary antigen tests for *L. pneumophila* and *S. pneumonia* (Level II evidence). For mechanically ventilated patients, an endotracheal aspirate should be cultured (Level II evidence). In selected, severely ill, CAP patients more aggressive diagnostic testing such as bronchoscopic sampling should be performed, determined on an individual basis (Level II evidence). In patients with persistent productive cough, significant weight loss, night sweats, or other risk factors for tuberculosis, a sputum sample for

acid-fast stain and TB cultures should be performed, and the patient kept in respiratory isolation (Level II evidence). For patients with significant pleural effusion, drainage and culture of pleural fluid may aid in obtaining etiologic diagnosis (Level II evidence).

FUTURE DATA AND VALIDATION

Reliance on an expatriate workforce brings to the region professionals with different training and backgrounds, magnifying the need for standardized methodologies in diagnostic microbiological testing of CAP in the GCC region.

REFERENCES

[1] Reimann HA. Landmark article Dec 24,1938: An acute infection of the respiratory tract with atypical pneumonia. A disease entity probably caused by a filtrable virus. By Hobart A. Reimann. JAMA 1984; 251(7): 936-44.

[2] Metlay JP, Schulz R, Li YH, Singer DE, Marrie TJ, Coley CM, et al. Influence of age on symptoms at presentation in patients with community-acquired pneumonia. Arch Intern Med 1997; 157(13): 1453-9.

[3] Riquelme R, Torres A, el-Ebiary M, Mensa J, Estruch R, Ruiz M, et al. Community-acquired pneumonia in the elderly. Clinical and nutritional aspects. Am J Respir Crit Care Med 1997; 156(6): 1908-14.

[4] Janssens JP. Pneumonia in the elderly (geriatric) population. Curr Opin Pulm Med 2005; 11(3): 226-30.

[5] Niederman MS, Ahmed QA. Community-acquired pneumonia in elderly patients. Clin Geriatr Med 2003; 19(1): 101-20.

[6] El Solh A, Pineda L, Bouquin P, Mankowski C. Determinants of short and long term functional recovery after hospitalization for community-acquired pneumonia in the elderly: role of inflammatory markers. BMC Geriatr 2006; 6: 12.

[7] El Solh AA, Aquilina AT, Gunen H, Ramadan F. Radiographic resolution of community-acquired bacterial pneumonia in the elderly. J Am Geriatr Soc 2004; 52(2): 224-9.

[8] Schmidt-Ioanas M, Lode H. Treatment of pneumonia in elderly patients. Expert Opin Pharmacother 2006; 7(5): 499-507.

[9] Marrie TJ, Blanchard W. A comparison of nursing home-acquired pneumonia patients with patients with community-acquired pneumonia and nursing home patients without pneumonia. J Am Geriatr Soc 1997; 45(1): 50-5.

[10] Tleyjeh IM, Tlaygeh HM, Hejal R, Montori VM, Baddour LM. The impact of penicillin resistance on short-term mortality in hospitalized adults with pneumococcal pneumonia: a systematic review and meta-analysis. Clin Infect Dis 2006; 42(6): 788-97.

[11] Global Action on Aging. http: //www.globalaging.org/index.htm.

[12] Campbell SG, Murray DD, Hawass A, Urquhart D, Ackroyd-Stolarz S, Maxwell D. Agreement between emergency physician diagnosis and radiologist reports in patients discharged from an emergency department with community-acquired pneumonia. Emerg Radiol 2005; 11(4): 242-6.

[13] Syrjala H, Broas M, Suramo I, Ojala A, Lahde S. High-resolution computed tomography for the diagnosis of community-acquired pneumonia. Clin Infect Dis 1998; 27(2): 358-63.

[14] Campbell SG, Marrie TJ, Anstey R, Ackroyd-Stolarz S, Dickinson G. Utility of blood cultures in the management of adults with community acquired pneumonia discharged from the emergency department. Emerg Med J 2003; 20(6): 521-3.

[15] Alves DW, Kennedy MT. Community-acquired pneumonia in casualty: etiology, clinical features, diagnosis, and management (or a look at the "new" in pneumonia since 2002). Curr Opin Pulm Med 2004; 10(3): 166-70.

[16] Mandell LA, Bartlett JG, Dowell SF, File TM, Jr., Musher DM, Whitney C. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis 2003; 37(11): 1405-33.

[17] van der Eerden MM, Vlaspolder F, de Graaff CS, Groot T, Bronsveld W, Jansen HM, et al. Comparison between pathogen directed antibiotic treatment and empirical broad spectrum antibiotic treatment in patients with community acquired pneumonia: a prospective randomised study. Thorax 2005; 60(8): 672-8.

[18] Niederman MS, Mandell LA, Anzueto A, Bass JB, Broughton WA, Campbell GD, et al. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 2001; 163(7): 1730-54.

[19] Amsden GW. Treatment of Legionnaires' disease. Drugs 2005; 65(5): 605-14.

[20] Jereb M, Kotar T. Usefulness of procalcitonin to differentiate typical from atypical community-acquired pneumonia. Wien Klin Wochenschr 2006; 118(5-6): 170-4.

[21] Nyamande K, Lalloo UG. Serum procalcitonin distinguishes CAP due to bacteria, *Mycobacterium tuberculosis* and PJP. Int J Tuberc Lung Dis 2006; 10(5): 510-5.

[22] Christ-Crain M, Stolz D, Bingisser R, Muller C, Miedinger D, Huber PR, et al. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. Am J Respir Crit Care Med 2006; 174(1): 84-93.

[23] Boussekey N, Leroy O, Alfandari S, Devos P, Georges H, Guery B. Procalcitonin kinetics in the prognosis of severe community-acquired pneumonia. Intensive Care Med 2006; 32(3): 469-472.

[24] Beovic B, Kreft S, Osredkar J, Kese D, Bonac-Tuma B. Serum procalcitonin levels in patients with mild community-acquired pneumonia. Clin Microbiol Infect 2005; 11(12): 1050-1.

[25] Masia M, Gutierrez F, Shum C, Padilla S, Navarro JC, Flores E, et al. Usefulness of procalcitonin levels in community-acquired pneumonia according to the patients outcome research team pneumonia severity index. Chest 2005; 128(4): 2223-9.

[26] Boussekey N, Leroy O, Georges H, Devos P, d'Escrivan T, Guery B. Diagnostic and prognostic values of admission procalcitonin levels in community-acquired pneumonia in an intensive care unit. Infection 2005; 33(4): 257-63.

[27] Franzin L, Cabodi D. Legionella pneumonia and serum procalcitonin. Curr Microbiol 2005; 50(1): 43-6.

[28] Christ-Crain M, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. Lancet 2004; 363(9409): 600-7.

[29] Polzin A, Pletz M, Erbes R, Raffenberg M, Mauch H, Wagner S, et al. Procalcitonin as a diagnostic tool in lower respiratory tract infections and tuberculosis. Eur Respir J 2003; 21(6): 939-43.

[30] Pimentel L, McPherson SJ. Community-acquired pneumonia in the emergency department: a practical approach to diagnosis and management. Emerg Med Clin North Am 2003; 21(2): 395-420.

REPRINT

Journal of Chemotherapy Vol. 19 - Supplement n. 1 (33-46) - 2007

Management and Prevention Strategies for Community-Acquired Pneumonia in the Gulf Corporation Council

Z.A. MEMISH [1] - Y.M. ARABI [2] - Q.A. AHMED [3] - A.M. SHIBL [4] - M.S. NIEDERMAN [5]
AND THE GCC CAP WORKING GROUP (GCC-CAPWG)

Departments of [1] Infection Prevention and Control, [2] Intensive Care Medicine, King Abdulaziz Medical City, Riyadh, Saudi Arabia, [3] Department of Medicine, Medical University of South Carolina, Charleston, South Carolina, USA, [4] Department of Microbiology, King Saud University Hospital, Riyadh, Saudi Arabia, [5] Department of Medicine, Winthrop-University Hospital, New York, USA

Corresponding author: Ziad A. Memish MD, FACP, FRCPC, FIDSA, Executive Director, Infection Prevention and Control, National Guard Health Affairs and Director, GCC Center for Infection Control, King Abdulaziz Medical City, Riyadh, P.O. Box 22490, Riyadh 11426, Kingdom of Saudi Arabia and Adjunct Professor of Medicine, University of Ottawa, Ottawa, Canada. Tel. No.: +966-1-2520088 x 43718; Fax No.: +966-1-2520437.
E-mail: zmemish@yahoo.com, memish@ngha.med.sa

Summary

Risk factors identify likelihood and severity of community-acquired pneumonia (CAP) and may allow prognostication. Prognostic factors can focus resources and efforts on those who may need special observation. Several risk assessment tools are used to estimate the severity of CAP and whether these tools can be used to predict outcomes, to determine disposition or even used to determine ICU level of care is hotly under debate. Treating CAP depends on age and comorbidities, as well as local epidemiology and disease severity. The current guidelines for managing CAP categorize patients with CAP into the healthy outpatient, the outpatient with modifying factors or comorbidities, the inpatient with CAP and patients requiring intensive care unit admission. These guidelines took into account regional bacteriology, antibiotic resistance data and available antibiotics to formulate recommendations. Preventive strategies for CAP include the administration of pneumococcal and influenza vaccine in selected populations at risk.

Key words: **Therapy, prevention, Hajj, guidelines, pneumonia, and community-acquired infection, Saudi Arabia, evidence-based medicine.**

THE ADMISSION AND SITE OF CARE DECISIONS

INTERNATIONAL PERSPECTIVE

Different tools have been used to estimate the severity of CAP [1]. Whether these tools should be used to predict outcomes, to determine disposition or even used to determine ICU level of care is hotly under debate [2]. Many tools are also limited in how readily they translate at the bedside in a real world setting.

The Pneumonia Severity Index (PSI) is complex and heavily weights age and comorbidity, dividing patients into 5 risk groups for mortality [3]. Classification is based on a two-step approach examining demographic factors, comorbidities, physical findings and investigative (laboratory and radiological) data. Patients under fifty years of age, with no comorbidities (including no malignancy) and no abnormal laboratory data or physical findings are class I according to the PSI. All others fall into Class II-V, based on age, gender, nursing home residency, comorbidities, physical examination and laboratory data. Each factor carries points and accumulated points score determines the PSI classification. In the derivation and validation of PSI, mortality ranged from 0.1 to 0.4% in Class I, 0.6 to 0.7% in Class II, and 0.9 to 2.8% in Class III, 8.2 to 9.3% in Class IV and 27.0 to 31.1% in Class V. It is hypothesized that patients in risk Class I or II be considered for outpatient

 ISSN 1120-009X

treatment. Patients in risk Class III are considered candidates for outpatient treatment or brief inpatient observation, while patients in Classes IV and V should be considered for traditional inpatient therapy. No attempt is made to define the need for admission to the ICU. Because of this age-weighting, the PSI exaggerates disease severity simply based on host age, overshadowing other factors. Furthermore it may also overestimate the need for expensive resources with an inappropriate emphasis on age and comorbidity and not on actual severity features. This is because the PSI was essentially developed to define LOW RISK patients, and often also underestimates the need for hospital or even ICU level of care.

Lim *et al* conducted three prospective inpatient CAP studies totaling 1068 patients. 80% of the study population was used as the derivation cohort and the remaining 20% for validation. The investigators found the following factors to be predictive of death: the presence of confusion, a serum BUN >7 mmol/L (>19 mg/dL), tachypnea greater than 30 breaths per minute, systolic hypotension under <90mm Hg or diastolic hypotension less than ≤60 mm Hg, age above 65 years, fever, and hypoalbuminemia of less than <30 g/dL. The acronym for these values was termed CURB: confusion, uremia, respiratory rate and blood pressure. One point was ascribed for each positive factor of CURB and an additional point for age greater than 65. This definition of pneumonia severity is also termed the CURB-65 score [4] (*Table 1*). Using these predictors, mortality is increased by 21-fold if three or more features are present on admission. This tool is chiefly applied to those presenting in an emergency room setting where initial laboratory data is available. Patients who have a CURB-65 score of 3 or more are at high risk of death and should be managed as having severe pneumonia. Patients who have a CURB-65 score of 2 are at increased risk of death. They should be considered for short stay inpatient treatment or hospital supervised outpatient treatment. This decision is a matter of clinical judgment. Patients who have a CURB-65 score of 0 or 1 are at low risk of death. They can be treated as having non-severe pneumonia and may be suitable for home treatment. If confusion is added to the factors above and is present in addition to two of three, mortality rises to a 36-fold increase.

In the outpatient settings where laboratory facilities may not be found, a modified version of CURB-65, can be used. This version, called CRB-65, has been validated in several studies (*Table 1*) [5-7].

Conceivably any clinician in an office setting will be able to make most of CURB-65 or CRB-65 measurements, making these tools very handy for almost all CAP patients assessed at the time of presentation.

Validation studies found that these clinical prediction rules for severe CAP have their limitations and therefore these rules do not replace clinical judgment [8 9]. The utility of CURB-65, for example, may be limited in the elderly and those with any comorbidity not accounted for in deriving the score.

Another limitation in using the pneumonia severity measures is the presence of other non-medical factors in the admission decision making. Lack of an appropriate caregiver of itself indicates hospitalization; similarly psychiatric disease and substance abuse are also indicative of admission for lower disease severity.

LOCAL PERSPECTIVE

There are no studies validating the use of CAP severity measures in the GCC region. However, because of its simplicity and practicality CURB-65 and CRB-65 seem more applicable in the GCC region than PSI. The importance of non-medical factors in the decision making for hospitalization is probably different in the GCC region compared to the West. Across the GCC region, where an the extended family is the norm rather than the exception of societal structure, lack of an appropriate caregiver is not a common indication - elderly GCC residents are generally attended to by their family until the end of life.

RECOMMENDATIONS

The decision to admit the CAP patient is agreed to be the single most defining decision a clinician takes in the entire disease course [10]. Admitting the patient to hospital activates more invasive testing and closer monitoring. This should be reserved for those deemed at higher risk of mortality. A simplified recommendation is illustrated in *Table 1*. CRB-65 should be used in outpatients and CURB-65 for hospitalized patients. In general, hospitalization is recommended for patients with CURB-65 score of ≥2 and ICU admission for those with score of ≥3 (Level II evidence). The CURB-65 is very good for avoiding overlooking severe illness. However, these rules do not replace clinical judgment (Level II evidence). Admission to an ICU is required for patients with septic shock requiring vasopressors or with acute respiratory failure requiring intubation and mechanical ventilation. (Level II evidence). Patients with suspected tuberculosis should be placed under respiratory isolation (Level II evidence).

FUTURE DATA AND VALIDATION INFORMATION

There is a need for validation of CAP severity measures in the GCC region. This will be only possible after developing a regional database for CAP.

TABLE 1 - *CURB-65 AND CRB-65 severity scores for CAP*

Clinical factor	**Points**
Confusion	1
Blood urea nitrogen >19 mg per dL BUN >7 mmol/L (>19 mg/dL)	1
Respiratory rate >30 breaths per minute	1
Systolic blood pressure <90 mm Hg or Diastolic blood pressure <60 mm Hg	1
Age >65 years	1
Total points	
CURB-65 score	**Recommendation**
0-1	Low risk; consider outpatient therapy
2	Short hospitalization or closely supervised outpatient therapy
3-5	Severe pneumonia; hospitalize and consider ICU admission
CRB-65 score *	**Recommendation**
0-1	Low risk; consider outpatient therapy
2	Consider hospitalization
3-4	Severe pneumonia; hospitalize and consider ICU admission

* A CRB-65 score is calculated by adding all the clinical factors except BUN

The future growth of the home healthcare in the region will have an impact on expanding outpatient therapy of CAP.

PATIENT STRATIFICATION AND EMPIRIC THERAPY

INTERNATIONAL PERSPECTIVE

Evaluation of any risk factors for certain pathogens (including drug resistant etiologies) and the presence of modifying circumstances increasing the patient's predisposition to infection, or inability to resolve CAP normally, must be considered from the outset of presentation.

Certain host factors increase the likelihood of infection with DRSP (*Table 2*). DRSP risks include age above 65 years, recent β-lactam therapy (within 3 months), alcoholism, immune suppression (including steroids), multiple medical co-morbidities, and exposure to children in day care facilities.

Patients with CAP should also be evaluated for risk factors for enteric gram negative organisms and pseudomonas as the presence of these factors will influence initial therapeutic choices. Gram-negative strains must be considered in the setting of underlying cardiopulmonary disease, multiple medical co-morbidities, and also recent antibiotic therapy (no specified time frame). CAP caused by *Pseudomonas aeruginosa* must be considered when structural lung disease is present, for example in those with bronchiectasis, current or recent corticosteroid use (>10 mg prednisone/day), prior broad-spectrum antibiotics for >7 days within the past month and malnutrition. Searching for these risk factors during the initial history taking will aid patient stratification. Finally, in patients who failed antibiotic therapy, other unusual pathogens such as viral or mycobacterial infections should be suspected (*Table 2*).

Recent antibiotic exposure has enormous impact on the presence of antibiotic resistance and is newly recognized as an independent risk factor for infection with enteric gram negatives. The Toronto Bacterial Infection Network was established to examine the effect of recent antibiotic exposure on subsequent pneumococcal resistance [11]. In their study of 3339 episodes of invasive pneumococcal infection, they found the use of beta-lactams, TMP/SMX, macrolides and quinolones predicted subsequent resistance. Also, quinolone resistance was much more likely if the patient was concomitantly on steroid therapy, or in the setting of nosocomial infection [11]. Recent antibiotic use therefore is an independent risk factor predicting drug resistance and a careful antibiotic history must be taken at initial presentation.

Armed with the knowledge of these factors, which could modify the patient's presentation and potential infecting agents and their potential susceptibilities, the clinician is best able to select a safe and inclusive treatment regimen from the outset. Additionally, assessing for these risk factors aids in decisions pertaining to the patient's initial disposition, whilst also allowing realistic expectations of

anticipated clinical and radiological resolution. The above are utilized as means of stratifying patients for recommended empiric therapy [10].

TABLE 2 - *Risk factors for certain pathogens. These risk factors are used as modifying factors in making treatment decisions.*

Risk factors for drug-resistant *S. pneumoniae*
• Age >65 yr
• Beta-lactam therapy within the past 3 months
• Alcoholism
• Immune-suppressive illness (including therapy with corticosteroids)
• Multiple medical comorbidities
• Exposure to a child in a day care center
• Recent antibiotic therapy in family member
Risks for enteric Gram-negative bacilli
• Structural lung disease
• Underlying cardiopulmonary disease
• Multiple medical comorbidities
• Recent antimicrobial therapy
• Failure of antibiotic therapy
Risks for Pseudomonas
• Structural lung disease
• Corticosteroid use (prednisone >10mg /day)
• Recent broad spectrum antimicrobials (more than 7 days in prior month)
• Malnutrition
Risks for viral and mycobacterial infections
• Failure of antibiotic therapy
• Exposure to mass gatherings (Hajj or Umra)

Current North American principles of antimicrobial therapy for the treatment of CAP include a number of distinct values, which are not encompassed in other regional guidelines and are important to note. The first dose of therapy must be administered rapidly (some guidelines and governmental agencies state within 4 hours of admission). Evidence supports starting antibiotic treatment within 4 hours of arrival at the hospital, and this has been recommended as a core quality and performance measure [12]. For those hospitalized for CAP, early antibiotic administration is clearly associated with improved inpatient and 30 day mortality [13,14]. Houck *et al* [15] performed a retrospective study using medical records from a national random sample of 18,209 Medicare patients older than 65 years who were hospitalized with CAP from July 1998 through March 1999. They found antibiotic administration within 4 hours of arrival at the hospital to be associated with reduced in-hospital mortality, mortality within 30 days of admission, and length of stay. As a result, it is a US Medicare "core measure " to give antiibotics within the first 6 hours of admission. The period of transfer from emergency room to the ward has been identified as vulnerable for discontinuity in antibiotic orders and is likely to be the next focus of scrutiny for improved care. Available guidelines and pocket flashcards will only improve the likelihood of administering the correct treatment at the correct dose as soon as the patient is hospitalized.

Every CAP patient must be empirically treated for atypical infection and pneumococcus, plus other pathogens dictated by a careful risk factor assessment. Monotherapy with macrolides is limited only to selected inpatients and those outpatients with no cardiopulmonary disease or modifying factors. Vancomycin/ linezolid must be always be used cautiously in the CAP population to avoid misuse. Monotherapy with quinolones for an ICU admitted CAP patient is never recommended as an empiric approach in those who are mechanically ventilated or in septic shock [16]. Also, North American guidelines allow for the observation that quinolones are not all alike with regard to pneumococcal activity and potential for selecting resistance and clinicians should make efforts to distinguish features of specific quinolones for use in their patients. Our therapeutic recommendations have incorporated many of these fundamentals.

Several classes of antimicrobials have been used in the management of CAP each has unique pharmacokinetic and pharmacodynamic characteristics that places each a unique role in the algorithm of CAP management.

Factors for consideration of specific antimicrobials include spectrum of activity, potential for inducing resistance, pharmacokinetics and pharmacodynamics, efficacy, safety and cost. The selection of specific antimicrobial regimens for empiric therapy is based largely on a number of principles outlined above, including the prediction of the most likely pathogens (aided by knowledge of commonly encountered pathogens in a geographic area and an appreciation of their usual susceptibilities patterns); and the presence of medical comorbidities that may influence the pathogen, increase likelihood for drug-resistant *S. pneumoniae.* (DRSP), and potentially be a risk factor for clinical failure (*Table 3*).

The respiratory fluoroquinolones (levofloxacin, moxifloxacin and gemifloxacin) have an important role in the management of CAP because of their ability to cover Gram-positive, Gram-negative, and atypical pathogens with a single agent [17-21]. There have been concerns about the association between the use of levofloxacin and the induction of resistance in pseudomonas species and *Streptococcus pneumoniae* [22], especially with the 500 mg dosing regimen per day compared with 750 mg per day. Quinolones penetrate well into the lung, often

achieving higher parencyhmal than serum levels. In addition, quinolones can be given once a day and are highly bioavailable, achieving similar serum levels with oral therapy as with intravenous therapy allowing for excellent 'step down' therapy without compromising bioavailability. These features allow for certain patients with moderately severe illness to be treated with oral therapy out of the hospital and also may permit the hospitalized patient to switch rapidly from intravenous to oral therapy, allowing for an early hospital discharge. There are some studies showing that admitted patients, even with bacteremia, can be effectively treated with an oral quinolone [23]. Concerns have been raised about the use of flouroquinolones as a first line therapy for CAP especially in areas where tuberculosis is considered endemic because it can potentially mask and delay the diagnosis of tuberculosis [24].

TABLE 3 - *Factors influencing the choice of antibiotic therapy of CAP*

Antibiotic factors
• spectrum of activity
• potential for inducing resistance
• pharmacokinetics and pharmacodynamics
• efficacy
• safety
• cost
Patient factors
• Co-morbidities
• Modifying factors
• Severity of pneumonia
Geographic factors
• Prevalence of resistant organisms
• Antibiotic availability and registration at the national and FDA level
• Pharmoeconomics

Currently available macrolides include erythromycin and new generation macrolides (azithromycin and clarithromycin). The use of erythromycin has fallen out of favor with the introduction of newer macrolides, due the common GI side effects and the need for frequent daily dosing. In addition, the newer drugs are preferred due to their greater activity against *Haemophilus influenzae.* There is poor correlation between *in vitro* macrolide susceptibility and clinical response of pneumococcal infection [25]. This is due to the high degree of macrolide penetration into respiratory secretions. A recent randomized, double blind, placebo-controlled study examined the effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers. The study found that use of clarithromycin, but not of azithromycin, selected for the erm (B) gene, which confers high-level macrolide resistance [26].

β-lactams are commonly used antibiotics in CAP because of the availability and safety. However, they lack activity against atypical pathogens. A number of β-lactam agents that can be used for initial empiric therapy, if the organism is penicillin susceptible or intermediately resistant, include oral therapy with second generation cephalosporins (cefuroxime, cefaclor, cefprozil), oral third generation cephalosporins (cefdinir and cefditoren-pivoxil), high-dose amoxicillin (1 g every 8 h), amoxicillin/clavulanate (875 mg twice daily) and intravenous therapy with cefotaxime, ceftriaxone or ampicillin/sulbactam. The role of cefuroxime in treatment of patients with CAP has been questioned especially in patients with pneumococcal bacteremia [27]. In addition in the treatment of the hospitalized CAP patient, cefuroxime does not provide any cost advantage over ceftriaxone because of frequent dosing.

Other agents can be used in the treatment of CAP. Vancomycin and linezolid should be reserved for patients with high-level resistance who are failing other therapies. Vancomycin is available only in parental form, the other agents in contrast are available in both oral and parental forms. Because of recent FDA concerns about increased risk of fatal hepatotoxicity and the withdrawal of two indications of telithromycin, it should only be used with extreme caution at this point for CAP patients [28, 29].

Certain agents that should *not* be used if DRSP is suspected, because of a possible lack of efficacy, include first-generation cephalosporins, cefaclor, loracarbef, and trimethoprim/ sulfamethoxizole.

General adherence to medications improves as dosing frequency decreases - compliance with once or twice daily medicines is much greater than when compared to 3 or 4 times daily medications. Patient adherence and clinical success (i.e. resolution of pneumonia) also influence microbial resistance patterns. Medicine that is well tolerated and treatment courses that are completed result in faster symptomatic relief and ultimately reduces the economic burden of CAP. Fluoroquinolones, some of which are once a day have already demonstrated low resistance and high effectiveness [30].

Combining intelligent regimens which maximize adherence with direction provided by critical pathways or 'care-maps' improves patient outcomes further and decreases costs even more [31]. Care maps have become integral to the daily practice of medicine in the USA and much of the world is following this trend. Care maps guide healthcare workers to quickly assess how an inpatient is progressing in his or her treatment and whether desired outcomes are

attained. The role of critical pathways has been studied in CAP with levofloxacin specifically in the CAPITAL Study (CAP Intervention Trial Assessing Levofloxacin) [32]. The CAPITAL study investigators found that a greater percentage of low risk CAP patients that presented to hospitals using a critical pathway were treated as outpatients without an increase in adverse clinical outcomes. The critical pathways therefore allowed more patients to be identified and safely managed as outpatient CAP [32].

Thus, while choice of agent in this example was monotherapy with a quinolone (acceptable for an outpatient CAP in most patients), it was the application of a clear cut care map which assisted in selecting patients appropriately and ultimately, reduced admissions and costs without adding adverse events. The choice of a single, readily bioavailable, well tolerated agent (increasing patient compliance) and the selection of patients appropriate for therapy with this agent multiplied the benefit of either approach used in isolation.

Increasingly calls for antibiotic stewardship are made spurring a new team approach towards limiting this challenge. Antimicrobial management teams need to be multidisciplinary - both to advise on selection of agent, duration of treatment and release data regarding local surveillance patterns, but also to provide feedback on the impact of local prescription patterns to the prescribers themselves. This dynamic interaction can stimulate education and development within the ranks of clinicians entrenched in habits of old or simply too busy to consider the choices they may be taking. The case for multidisciplinary teams managing antimicrobial therapy for nosocomial infection is clear, but the principles for these arguments hold true when treating CAP also. The prevalence of antimicrobial resistance in the community and in the nosocomial environment is related to the selection of resistant organism by antibiotic exposure, plasmid transfer between bacterial strains and clonal spread of resistant organisms among the hospitalized and even between institutions. Ultimately these organisms can seep into the community itself: with CA-MRSA, we are now seeing a previously nosocomial organism expanding unabated into the community [33-39].

The duration of CAP therapy remains under debate [30,40,41]. CAP has traditionally been treated with a 7-14-day course of antimicrobial therapy. However, there has been no consensus on length of therapy among different organizational guidelines. Several recent studies have demonstrated that shorter course antibiotic regimens are as effective as longer courses [42,43]. The Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults recommends that patients with CAP should be treated for a minimum of 5 days, should be afebrile for 48-72 h, and should have no signs of clinical instability before discontinuation of therapy [44]. A longer duration of therapy may be needed if initial therapy was not active against the identified pathogen or if it was complicated by extrapulmonary infection, such as meningitis or endocarditis [44].

LOCAL PERSPECTIVE

Microbiology and resistance patterns are covered earlier. Drug resistance including DRSP is a challenge in the GCC region just as in other parts of the world. While data is scant on the modifying factors for CAP from the GCC region, the GCC CAPWP agreed that internationally identified modifying factors are applicable to the CAP patients in the region. In addition, the GCC CAPWP identified recent Hajj or Umra attendance as a modifying factor for CAP which should raise suspension for viral or mycobacterial etiology (*Table 2*). Major classes of antibiotics used in the treatment of CAP are available locally.

RECOMMENDATIONS

The central goal of these guidelines is to provide the practicing physician with an approach to the *initial antimicrobial management* of CAP. It should be mentioned that treatment guidelines are empiric in nature and antibiotics should be started within 6 hours of presentation (Level II evidence). Once the causative pathogen is isolated and antibiotic susceptibility testing results are known, the antibiotic regimen should be tailored accordingly.

In devising these guidelines we used an approach similar to our previous guidelines and is based on an assessment of place of therapy (outpatient, hospital ward, or ICU) and the presence of modifying factors [45] (*Table 2*). These modifying factors include the presence of risk factors for DRSP, the presence of risk factors for enteric Gram-negative bacilli, and the presence of risk factors for *P. aeruginosa* as outlined above. 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. Once hospitalization occurs, DRSP risks must always be considered, both in the ward patient and in the ICU. The diagnostic work up remains unchanged, and no evidence exists that the suspicion of DRSP should require additional testing. Atypical pathogen infection should be considered in all patient groups, sometimes in the form of mixed infection (Level II evidence).

The issue of using fluoroquinolones as a first line therapy for CAP in the settings of high prevalence of tuberculosis was discussed by the GCC CAPWG. It was felt that fluoroquinolones can still be used as a first line therapy in CAP in the general population. However, in CAP patients presenting with features

suggestive of tuberculosis or in patients who failed to respond rapidly to CAP therapy, fluoroquinolones should be avoided (Level III evidence).

All patients fall into one of four groups, and each group is associated with a list of likely etiologic agents and suggested empiric therapy aimed at these potential pathogens (Level II and III evidence) (*Table 4*). This stratification of patients allows for a graded response in terms of the empiric therapy regimen selected. A less aggressive and narrower spectrum approach can be used for the milder cases, and as host factors become more complex or the severity of illness increases, a more aggressive and broad-spectrum regimen is recommended.

The GCC CAPWG took into account regional bacteriology, antibiotic resistance data and available antibiotics to formulate these recommendations.

Outpatient therapy

Outpatient therapy is considered in two groups, those with and those without comorbidities and or modifying factors.

The outpatient with no modifying risks of comorbidities can be treated as an outpatient with a single advanced generation macrolide, which would include azithromycin and clarithromycin (Level II evidence). Often these agents are once daily, 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 (Level II evidence). A 2.0 grams single dose of the newly licensed extended release azithromycin can be used in mild to moderate CAP (Level II evidence) [46,47].

The outpatient with modifying factors receives

TABLE 4 - *Recommendations for CAP therapy.*

Group	Common Pathogens	Recommended Therapy
Outpatient – no modifying risk factors	*Streptococcus pneumoniae* *Mycoplasma pneumoniae* *Chlamydophila pneumoniae* *Legionella pneumophila* *Haemophilus influenzae* Respiratory viruses	Advanced generation macrolide: azithromycin or clarithromycin **Or** Doxycycline
Outpatient – modifying risk factors	*Streptococcus pneumoniae* (including DRSP) *Mycoplasma pneumoniae* *Chlamydophila pneumoniae* *Legionella pneumophila* *Haemophilus influenzae* (including β-lactamase producing H. *influenzae)* Enteric Gram-negatives Respiratory viruses	Respiratory fluoroquinolone **Or** β-lactam *plus* an advanced generation macrolide
Inpatients, non-ICU	*Streptococcus pneumoniae* (Including DRSP) *Haemophilus influenzae* *Mycoplasma pneumoniae* *Chlamydophila pneumoniae* *Legionella pneumophila* Enteric Gram-negatives Respiratory viruses	Respiratory fluoroquinolone **Or** β-lactam *plus* an advanced generation macrolide **Or** Doxycycline *plus* β-lactam
Inpatients, ICU **No risk factors for *P. aeruginosa* or MRSA**	*Streptococcus pneumoniae* (including DRSP) *Legionella pneumophila* *Haemophilus influenzae* Enteric Gram-negative bacilli *Staphylococcus aureus* *Mycoplasma pneumoniae* Respiratory viruses	β-lactam **plus** either advanced generation macrolide **or** a respiratory fluoroquinolone
Risk factors for *P. aeruginosa*	*As above and Pseudomonas aeruginosa*	Two antipseudomonal agents from different classes **plus** advanced generation macrolide
Risk factors for *MRSA*	*As above and MRSA*	Add vancomycin **or** linezolid

monotherapy with respiratory fluoroquinolone or a β-lactam with an advanced generation macrolide (Level II evidence). This regimen provides excellent coverage of both typical (S. *pneumoniae*, *H. influenzae*, *M. catarrhalis*) including DRSP, β-lactamase producing H. *influenzae*, M. *catarrhalis* and atypical pathogens (*Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Legionella pneumophila*). In fact, in certain compliant patients who have access to the office, intravenous ceftriaxone may be an option and can be switched to oral third generation cephalosporin after 24 to 48 hours.

Inpatient therapy

Inpatient therapy must also be stratified by comorbidities and severity. For CAP patients admitted to the ward, empiric treatment is with respiratory fluoroquinolone monotherapy or a third-generation cephalosporin with a macrolide (Level II evidence). This regimen provides broad spectrum activity against both typical and atypical respiratory pathogens, many gram-negative bacilli and penicillin-intermediate resistant S. *pneumoniae*. Monotherapy with intravenous azithromycin is as effective as traditional β lactam/macrolide combinations in selected patients [48] (Level II evidence). 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 and a thoracic surgical opinion should be sought when indicated (Level III evidence).

The severely ill CAP patients requiring ICU admission need empiric therapy for pneumococcus, Legionella, and *H. influenzae* but risk of pseudomonal infection must always be assessed since pseudomonas CAPs presents in certain groups of patients as outlined previously (Level II evidence).

For CAP ICU patients without pseudomonal or MRSA risk factors, the recommended antimicrobial treatment is a combination of a beta-lactam plus a respiratory flouroquinlone or a macrolide (Level II evidence). Respiratory 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 (Level II evidence). When pseudomonal risk factors exist, two antipseudomonal agents from different classes should be used, in addition to coverage for DRSP and atypical pathogens. These two requirements can be met with the selected beta lactams as pipracillin-tazobactam, cefepime or carbapenems (Level II evidence).

CAP due to MRSA should be suspected in patients with severe CAP or post-influenza CAP and anti MRSA agents, such as vancomycin, linezolide or clindamycin should be added (Level II evidence) [49,50].

Short-course antibiotic therapy is equivalent to standard length of therapy for clinical cure and bacterial eradication (Level II evidence). Adults should be treated for a minimum of 5 days, should be afebrile for 48-72 hours and have no signs of clinical instability before discontinuing therapy (Level II evidence).

FUTURE DATA AND VALIDATION

The GCC CAPWG recommends a comprehensive system of implementing CAP guidelines at levels of healthcare along with establishing a monitoring system to assess the effectiveness and impact of following these recommendations. One strategy for implementation is to incorporate theses guidelines in national and regional clinical pathways for CAP management.

NATURAL HISTORY OF CAP: TAILORING THERAPY ACCORDING TO CLINICAL RESPONSE

INTERNATIONAL PERSPECTIVE

Normal resolution of pneumonia is not easily defined and varies according to the underlying etiology. An understanding of the expected course is important in assessing the patient's response to therapy. Knowing the expected course of therapy will avoid unnecessary change or escalation of therapy and over investigation. For instance, presence of fever in a patient who is otherwise clinically improving does not necessarily represent failure of therapy. Fever can be expected for the first 4 days of CAP. Most patients report subjective improvement within 3 to 5 days of initiation of therapy. Specific clinical criteria for resolution include improvement in fever, cough, crackles, leukocytosis, arterial oxygenation (PaO_2), and level of C-reactive protein.

The course of CAP can be divided into three stages [10]. The initial period begins with the onset of anti-microbial therapy for a further 24-72 hours during which the patient's clinical condition stabilizes and shows signs of improvement. The second period begins after 72 hours following which physical examination laboratory data and usually radiological imaging show objective improvement (unless reasons for delayed radiological resolution are present). Finally the patient enters the recovery period which may take further days to weeks, when the patient returns to his usual state of pre morbid health.

Most data concerning the natural history of pneumonia have focused on radiological resolution. Abnormal radiology persists longer than clinical abnormalities present on examination: this radiological lag is well recognized and therefore the initial x-ray may first worsen before improvement. Those with delayed radiological resolution are identified as patients with persisting radiographic abnormalities for greater than one month.

A number of factors retard healing of lung injury

due to pneumonia. These factors include comorbidities such as underlying cardiopulmonary disease, renal disease, diabetes and structural lung disease. Alcoholism and neurological conditions also contribute to delayed resolution with x-ray abnormalities persisting well beyond four weeks. Finally, pneumonia in those with human immunodeficiency virus (HIV) infection and malignancy are also expected to have delayed resolution.

CAP in the elderly not only presents differently (as discussed earlier) but is also associated with slower resolution [51-54]. Ninety percent of patients younger than 50 years of age show radiographic resolution by 4 weeks, compared with only 30% of patients older than 50, even in the absence of concurrent disease [51, 55]. Additionally the rate of resolution depends on the etiologic pathogen with resolution being more rapid with *Mycoplasma pneumoniae*, non-bacteremic *S pneumoniae, Chlamydophila* species, and *Moraxella catarrhalis* than with other organisms.

Decisions to switch therapy from parenteral to enteral routes and to complete course of antibiotics are based on an assessment of the patient's clinical course, an intact enteral system and social factors that support discharge to community. Patients can be divided into three categories, those with early response, those lacking response (assessed after the third day of treatment) and those with active deterioration. Early responders should be quickly changed to oral therapy provided there is no question of ability to absorb enterally. Discharge can follow quickly. Earlier studies reported i.v.-p.o. switch after 3-4 days [56,57] but more recent data suggest that the switch can be performed after 1-3 days of intravenous therapy [58]. 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 [32,56,57]. The remainder need to be evaluated carefully to see if factors accounting for a longer course are to be expected including the presence of comorbidities, immune suppression or structural lung disease. Most experts recommend that parentral therapy be switched to oral therapy in no earlier than three days in patients who can tolerate oral therapy and show clinical stability [59].

Clinical *and* radiological deterioration in parallel warrant aggressive investigation and reassessment of the patient's disposition which may require more intensive monitoring and transfer to a critical care area [10].

Mortality from CAP remains unchanged over the past two decades, perhaps because prevalence of the disorder is increasing along with growing numbers of elderly and immuno-suppressed patients despite advance of therapy and recognition of this condition. One could also hypothesize that increasing rates of drug resistance also impact on our failure to modify pneumonia-related mortality. A prospective study looking at prognostic factors for bacteremic pneumoccocal CAP in five countries found mortality to range from 6% in Canada, 20% in the USA and Spain and 13% in the UK and 8% in Sweden [60]. Age greater than 65 years was an independent risk factor along with underlying chronic lung disease, elevated APACHE scores and need for invasive mechanical ventilation. Mortensen *et al* have identified that half of deaths attributable to CAP result from a worsening of underlying co morbidities [61]. In an Asian study on pneumococcal pneumonia, bacteremia and mechanical ventilation were significant risk factors for death, but any kind of antibiotic resistance was not associated with increased mortality [62]. In a study of 245 patients with CAP, tachypnea, diastolic hypotension, and an elevated blood urea nitrogen were independently associated with death from pneumonia in our study, confirming the value of a previously reported discriminant rule from the British Thoracic Society [63]. In CAP patients admitted to the ICU, septic shock was found to have the highest association with mortality [64].

The Pneumonia Patient Outcomes Research Team cohort study evaluated the causes of death in CAP patients[61]. Among 944 outpatients and 1343 inpatients with CAP, 208 (9%) died by 90 days. The most frequent immediate causes of death were respiratory failure (38%), cardiac conditions (13%), and infectious conditions (11%); the most frequent underlying causes of death were neurological conditions (29%), malignancies (24%), and cardiac conditions (14%). Mortality was pneumonia related in only 110 (53%) of the 208 deaths. Factors independently associated with pneumonia-related mortality were hypothermia, altered mental status, elevated serum urea nitrogen level, chronic liver disease, leukopenia, and hypoxemia. Factors independently associated with pneumonia-unrelated mortality were dementia, immunosuppression, active cancer, systolic hypotension, male sex, and multilobar pulmonary infiltrates. Increasing age and evidence of aspiration were independent predictors of both types of mortality [61].

LOCAL PERSPECTIVE

The importance of *Mycobacterium tuberculosis* as an etiologic agent for CAP in Saudi Arabia has been discussed before [65,66]. *M. tuberculosis* was the most common pathogen recovered among hospitalized CAP population during Hajj in one study [66]. There are no data on the response rate or pattern of CAP in the GCC region.

RECOMMENDATIONS

Normal resolution of pneumonia is not easily defined and varies according to the underlying etiology. Most patients report subjective improvement

within 3 to 5 days of initiation of therapy. However, radiological improvement usually lags behind. Early responders who can tolerate oral therapy should be changed to oral therapy in no earlier than three days of parenteral therapy as long as they show clinical stability (Level II evidence).

FUTURE DATA COLLECTION AND VALIDATION

Larger scale studies are needed to examine the importance of tuberculosis as a cause of non-resolving CAP. There is also a need for evaluation of rate of response in relation to genetic polymorphisms in the inflammatory response that are common in the GCC region.

CAP DURING HAJJ
LOCAL PERSPECTIVE

Specific comment on CAP during Hajj is warranted because so many of the residents of the GCC will be exposed to returning or worshipping pilgrims during the largest religious mass migration in the world which recurs annually. A prospective study performed in two hospitals during Hajj found respiratory diseases to be the most common causes of hospitalization (57%) with pneumonia being the leading reason for hospitalization in 39% of all patients [67].

Another study examined the pathogens of CAP during the 1994 Hajj [66].Data was collected from patients admitted to Al-Noor Specialist Hospital and King Abdul Aziz hospital in Makkah between 3-28th May 1994. Bacteriological diagnosis was confirmed in 72% of patients (n=46*). Mycobacterium tuberculosis* was the most common pathogen recovered among this hospitalized CAP population (20%). If validated in other studies, this finding may have profound implications on the diagnostic approach, empiric therapy and infection control of CAP during Hajj. Until more evidence emerges, clinicians must keep a high index of suspicion for tuberculosis (TB) in pilgrims presenting with CAP.

The use of fluoroquinolones as first line therapy in CAP during Hajj may cause a delay in the diagnosis of tuberculosis and may also promote the development of resistance. However, this concern has been reported in one case report (Level III evidence) [68].

RECOMMENDATIONS

The GCC CAPWG adopts the Saudi MOH recommendation that influenza vaccination to pilgrims attending Hajj, especially those with underlying chronic illnesses such as cardiopulmonary disease and is mandatory for all healthcare workers working in Makkah and Madinah, the sites of worship during the Hajj (Level II evidence).

The GCC CAPWG also endorses the Saudi MOH recommendation for the use of facemasks during Hajj, to reduce airborne transmission of disease [69] (Level III evidence). Compliance with this recommendation has been poor. A 1999 survey by the MOH during Hajj found facemask compliance rates of 24% [70]. Though data on efficacy of facemask use in prevention of RTI at Hajj is lacking, it is a simple, inexpensive and innocuous recommendation to make. All pilgrims (many of whom will be traveling from areas of low TB endemicity) would be well advised to conduct the Hajj wearing facemasks.

In treatment of CAP during Hajj, the use of fluoroquinolones as a first line therapy should be avoided because of concerns of masking and delaying tuberculosis diagnosis (Level III evidence).

PREVENTION AND CONTROL

INTERNATIONAL PERSPECTIVE

Influenza vaccination has been shown to reduce illness and all-cause mortality in vulnerable populations and to improve survival in hospitalized patients with CAP during influenza season [71]. Two types of influenza vaccine, an inactivated and live attenuated influenza vaccines (LAIV) are available. Although both types of vaccines are effective, the vaccines differ in several aspects. Both LAIV and inactivated influenza vaccines contain strains of influenza viruses that are antigenically equivalent to the annually recommended strains. Viruses for both vaccines are grown in eggs and are administered annually. Because inactivated influenza vaccine contains killed viruses it does not produce influenza signs or symptoms. In contrast, LAIV can produce mild influenza manifestations. LAIV is administered intranasally by sprayer, whereas inactivated influenza vaccine is administered intramuscularly by injection.

Pneumococcal polysaccharide vaccine reduces the incidence of CAP and bacteremic pneumococcal disease in particular [72,73]. In addition, prior vaccination against pneumococcus was associated with improved survival, decreased chance of respiratory failure or other complications, and decreased length of stay among hospitalized patients with community-acquired pneumonia [73]. Currently, there are 2 vaccines available, 23 valent polysacharide vaccine, representing approximately 90% of all serotypes that cause invasive pneumococcal disease in the adult population. The other vaccine is a 7-valent conjugate formulation especially designed for pediatric use, which is beyond the scope of this document. Studies have shown that the 23-valent vaccine prevented pneumococcal pneumonia (with or without bacteremia) and decreased the rates of overall pneumonia and of mortality due to pneumonia in older adults [74]. Post licensure epidemiological studies have documented the value of the 23 valent pneumococcal vaccine in preventing invasive infection among

elderly and younger adults with some chronic medical condition in about 45-75%. The vaccine has been shown to be cost-effective for general populations of adult as well as elderly [75,76].

LOCAL PERSPECTIVE

Both Frayha and Al Mazrou and Memish *et al* have demonstrated a very good distribution (86%) of the local serotypes in Saudi Arabia in the 23 valent polysaccharide pneumococcal vaccine [77,78]. However, a similar study by Ahmed *et al* showed that only 63% of the circulating serotypes and specifically 57% of those from CSF and blood in Kuwait are covered by the 23 valent pneumococcal vaccine [79]. However, the vaccine clinical effectiveness in prevention of CAP has not been studied in the GCC region, though there is no reason to believe that these vaccines would be any less efficacious than what has been reported elsewhere.

The role of other vaccines in CAP prevention includes varicella vaccine since a significant percentage of the adult GCC population is susceptible to VZV infection [80-87]. This has lead to the recent addition of VZV vaccine to the expanded program of immunization (EPI) in Saudi Arabia and Qatar.

RECOMMENDATIONS

The GCC CAPWG adopts the recommendations of the Advisory Committee on Immunization Practices (ACIP) for annual administration of inactivated influenza vaccine for persons at high risk for influenza-related complications and severe disease, including persons of any age with certain chronic medical conditions, persons aged ≥50 years, pregnant women, persons who live with or care for persons at high risk (household contacts) and health-care workers [88]. Live attenuated influenza vaccine is an option for vaccination of healthy, non-pregnant persons aged 5-49 years, and those who might be in close contact with persons at high risk for severe complications, including health-care workers [88]. The GCC CAPWG endorses these recommendations (Level II evidence). In addition, influenza vaccine is recommended for adults who are going to perform Hajj and Umrah [69, 89-91] (Level III evidence). Pneumococcal polysacharide vaccine is recommended for specific high risk groups including chronic cardiovascular, renal or liver disease, cerebrospinal fluid leaks, asplenia, immunecompromised conditions, long term care facility residents and specially for chronic pulmonary disease and diabetes mellitus patients (Level II evidence).

VZV vaccine is recommended for susceptible adults to VZV infection (Level II evidence).

Considering the high prevalence of TB in the region, strict adherence to the international guidelines for prevention of spread of TB must be observed at all times [92,93] (Level II evidence).

FUTURE DATA COLLECTION AND VALIDATION

Studies are in progress to determine the serotypes/serogroups of invasive pneumococcal disease in the GCC region from adult patients and their antibiotic susceptibility in order to further explore the impact of the 23 valent polysaccharide pneumococcal vaccine in reducing the burden of pneumococcal disease in susceptible adult population. Similarly, there is a need to include the GCC countries in the WHO annual surveillance of influenza strains circulating in these countries to ensure that they are included in the vaccine strains.

CONCLUSION

Globally, guideline publication continues at a frenetic pace. Clinicians are anxious for ways to assess their own conformity to prevailing accepted standards. Institutions and third party bodies remain keen to make similar measurements between providers. In the GCC region presently there is an active drive for facilities to achieve credentialing with the international equivalent of JCAHO, a clear sign that institutes wish to compare themselves with others on the basis of common denominators. This healthy competition can only improve outcomes and processes rendered in the care of our patients.

The burden of respiratory disease in the GCC region will only increase, particularly with the graying of the regional population. Recent outbreaks such as SARS only serve to demonstrate how much more work is needed to prevent, rapidly diagnose and treat patients with severe CAP in the context of new epidemics. The forthcoming threat of an influenza epidemic carries similar anxieties, for patients will present in even greater numbers. The possibility of the influenza season eclipsing with the Hajj season is especially of concern to the GCC region, who accommodate the migration fluxes of returning pilgrims magnifying the risk of transmitting pathogens to their home countries which may trigger local outbreaks.

While new antibiotic development is important, far outweighing this is the need to use the existing armamentarium we have wisely and well. Wealthy countries such as the members of GCC are perhaps more vulnerable to the misguided belief that there will always be a bigger, better, newer antimicrobial emerging and to therefore push today's worries onto tomorrow. Relatively smaller populations, intermittently unregulated prescribing patterns, an ability to procure and deploy newer drugs *faster* through greater purchasing power with fewer bureaucratic challenges in this region sustain this naïve fallacy and fuel a false sense of security which must be dispelled. Clinicians throughout the GCC region must be re-acquainted with the responsibility that prescribing brings, a connection divorced from self in many practitioners. We all have a part to play in the glob-

al rise of antimicrobial resistance and antibiotic misuse. Thus, there is much room for improvement not only in which antibiotics are used but also *how* antibiotics are used. Managing a common clinical condition such as CAP with better principles and more attention to detail are worthy efforts for GCC clinicians to work towards.

These guidelines, when disseminated and implemented, aim to raise awareness of treatment algorithms for the CAP patient, will influence choice of agent, lower costs of therapy and shorten or even avert hospitalization, ultimately improving outcomes in the management of CAP in GCC patients.

Whether this is actually accomplished will be topics of future debate but until then for clinicians and CAP patients in the GCC, this is our beginning: a beginning towards better CAP management; a beginning towards greater vigilance of the evolving microbial flora of the region and most significantly the beginning of vigorous intellectual collaboration, both within the GCC region and with friends beyond the Peninsula.

By using the Internet, clinicians can build virtual teams which execute multicenter international projects more easily, faster, and less expensively than in the past, thus facilitating progress. Making large international databases available to investigators from around the world will greatly expand the possibilities to obtain new knowledge in the areas of community-acquired pneumonia (CAP) research and quality. By closing the gap between clinical research and clinical practice, the management of patients with CAP will improve worldwide [94].

REFERENCES

[1] Ioachimescu OC, Ioachimescu AG, Iannini PB: Severity scoring in community-acquired pneumonia caused by *Streptococcus pneumoniae*: a 5-year experience. Int J Antimicrob Agents 2004, 24(5):485-490.

[2] Niederman MS, Feldman C, Richards GA: Combining information from prognostic scoring tools for CAP: an American view on how to get the best of all worlds. Eur Respir J 2006, 27(1):9-11.

[3] Fine MJ, Auble TE, Yealy DM, Hanusa BH, Weissfeld LA, Singer DE, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. N Engl J Med 1997, 336(4):243-250.

[4] Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 2003, 58(5):377-382.

[5] Man SY, Lee N, Ip M, Antonio GE, Chau SS, Mak P, et al: Prospective comparison of three predictive rules for assessing severity of community acquired pneumonia in Hong Kong. Thorax 2006.

[6] Capelastegui A, Espana PP, Quintana JM, Areitio I, Gorordo I, Egurrola M, Bilbao A: Validation of a predictive rule for the management of community-acquired pneumonia. Eur Respir J 2006, 27(1):151-157.

[7] Bauer TT, Ewig S, Marre R, Suttorp N, Welte T: CRB-65 predicts death from community-acquired pneumonia. J Intern Med 2006, 260(1):93-101.

[8] Buising KL, Thursky KA, Black JF, MacGregor L, Street AC, Kennedy MP, Brown GV: A prospective comparison of severity scores for identifying patients with severe community acquired pneumonia: reconsidering what is meant by severe pneumonia. Thorax 2006, 61(5):419-424.

[9] Angus DC, Marrie TJ, Obrosky DS, Clermont G, Dremsizov TT, Coley C, et al. Severe community-acquired pneumonia: use of intensive care services and evaluation of American and British Thoracic Society Diagnostic criteria. Am J Respir Crit Care Med 2002, 166(5):717-723.

[10] Niederman MS, Mandell LA, Anzueto A, Bass JB, Broughton WA, Campbell GD, et al: Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 2001, 163(7):1730-1754.

[11] Vanderkooi OG, Low DE, Green K, Powis JE, McGeer A: Predicting antimicrobial resistance in invasive pneumococcal infections. Clin Infect Dis 2005, 40(9):1288-1297.

[12] Barlow G, Nathwani D, Williams F, Ogston S, Winter J, Jones M, et al: Reducing door-to-antibiotic time in community-acquired pneumonia: Controlled before-and-after evaluation and cost-effectiveness analysis. Thorax 2007, 62(1):67-74.

[13] Niederman MS, Ahmed QA: Community-acquired pneumonia in elderly patients. Clin Geriatr Med 2003, 19(1):101-120.

[14] Pimentel L, McPherson SJ: Community-acquired pneumonia in the emergency department: a practical approach to diagnosis and management. Emerg Med Clin North Am 2003, 21(2):395-420.

[15] Houck PM, Bratzler DW, Nsa W, Ma A, Bartlett JG: Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. Arch Intern Med 2004, 164(6):637-644.

[16] Leroy O, Saux P, Bedos JP, Caulin E: Comparison of levofloxacin and cefotaxime combined with ofloxacin for ICU patients with community-acquired pneumonia who do not require vasopressors. Chest 2005, 128(1):172-183.

[17] Balkhy HH, Memish ZA, Shibl A, Elbashier A, Osoba A: In vitro activity of quinolones against *S. pneumoniae, H. influenzae* and *M. catarrhalis* in Saudi Arabia. East Mediterr Health J 2005, 11(1-2):36-44.

[18] Amsden GW: Treatment of Legionnaires' disease. Drugs 2005, 65(5):605-614.

[19] Kraus CN, Zalkikar J, Powers JH: Levofloxacin and macrolides for treatment of legionnaires disease: multiple comparisons give few answers. Clin Infect Dis 2005, 41(3):416; author reply 416-417.

[20] Sabria M, Pedro-Botet ML, Gomez J, Roig J, Vilaseca B, Sopena N, Banos V: Fluoroquinolones vs macrolides in the treatment of Legionnaires disease. Chest 2005, 128(3):1401-1405.

[21] Moran G: Approaches to treatment of community-acquired pneumonia in the Emergency Department and the appropriate role of fluoroquinolones. J Emerg Med 2006, 30(4):377-387.

[22] Drago L, De Vecchi E, Nicola L, Tocalli L, Gismondo MR: In vitro selection of resistance in *Pseudomonas aeruginosa* and *Acinetobacter* spp. by levofloxacin and ciprofloxacin alone and in combination with beta-lactams and amikacin. J Antimicrob Chemother 2005, 56(2):353-359.

[23] Bernstein JM: Treatment of community-acquired pneumonia—IDSA guidelines. Infectious Diseases Society of America. Chest 1999, 115(3 Suppl):9S-13S.

[24] Singh A: Fluoroquinolones should not be the first-line antibiotics to treat community-acquired pneumonia in areas of tuberculosis endemicity. Clin Infect Dis 2007, 45(1):133; author reply 134-135.

[25] Shibl AM: Patterns of macrolide resistance determinants

among *S. pyogenes* and *S. pneumoniae* isolates in Saudi Arabia. J Int Med Res 2005, 33(3):349-355.

[26] Malhotra-Kumar S, Lammens C, Coenen S, Van Herck K, Goossens H: Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study. Lancet 2007, 369(9560):482-490.

[27] Waterer GW, Somes GW, Wunderink RG: Monotherapy may be suboptimal for severe bacteremic pneumococcal pneumonia. Arch Intern Med 2001, 161(15):1837-1842.

[28] Soreth J, Cox E, Kweder S, Jenkins J, Galson S: Ketek—the FDA perspective. N Engl J Med 2007, 356(16):1675-1676.

[29] Ross DB: The FDA and the case of Ketek. N Engl J Med 2007, 356(16):1601-1604.

[30] Segreti J, House HR, Siegel RE: Principles of antibiotic treatment of community-acquired pneumonia in the outpatient setting. Am J Med 2005, 118 Suppl 7A:21S-28S.

[31] Marrie TJ: Experience with levofloxacin in a critical pathway for the treatment of community-acquired pneumonia. Chemotherapy 2004, 50 Suppl 1:11-15.

[32] Marrie TJ, Lau CY, Wheeler SL, Wong CJ, Vandervoort MK, Feagan BG: A controlled trial of a critical pathway for treatment of community-acquired pneumonia. CAPITAL Study Investigators. Community-Acquired Pneumonia Intervention Trial Assessing Levofloxacin. Jama 2000, 283(6):749-755.

[33] Drews TD, Temte JL, Fox BC: Community-associated methicillin-resistant *Staphylococcus aureus*: review of an emerging public health concern. Wmj 2006, 105(1):52-57.

[34] Pfaller MA, Jones RN: Gatifloxacin phase IV surveillance trial (TeqCES study) utilizing 5000 primary care physician practices: report of pathogens isolated and susceptibility patterns in community-acquired respiratory tract infections. Diagn Microbiol Infect Dis 2002, 44(1):77-84.

[35] Enayet I, Nazeri A, Johnson LB, Riederer K, Pawlak J, Saravolatz LD: Community-associated methicillin-resistant *Staphylococcus aureus* causing chronic pneumonia. Clin Infect Dis 2006, 42(7):e57-60.

[36] Levison ME, Fung S: Community-associated methicillin-resistant *Staphylococcus aureus*: reconsideration of therapeutic options. Curr Infect Dis Rep 2006, 8(1):23-30.

[37] Frazee BW, Salz TO, Lambert L, Perdreau-Remington F: Fatal community-associated methicillin-resistant *Staphylococcus aureus* pneumonia in an immunocompetent young adult. Ann Emerg Med 2005, 46(5):401-404.

[38] Slama TG, Amin A, Brunton SA, File TM, Jr., Milkovich G, Rodvold KA, et al. A clinician's guide to the appropriate and accurate use of antibiotics: the Council for Appropriate and Rational Antibiotic Therapy (CARAT) criteria. Am J Med 2005, 118 Suppl 7A:1S-6S.

[39] Balkhy HH, Memish ZA, Almuneef MA, Cunningham GC, Francis C, Fong KC, et al: Methicillin-Resistant *Staphylococcus aureus*: a 5-year review of surveillance data in a tertiary care hospital in Saudi Arabia Infect Control Hosp Epidemiol 2007, 28:976-982.

[40] Scalera NM, File TM, Jr.: How long should we treat community-acquired pneumonia? Curr Opin Infect Dis 2007, 20(2):177-181.

[41] Qazi S: Short-course therapy for community-acquired pneumonia in paediatric patients. Drugs 2005, 65(9):1179-1192.

[42] Kuzman I, Dakovic-Rode O, Oremus M, Banaszak AM: Clinical efficacy and safety of a short regimen of azithromycin sequential therapy vs standard cefuroxime sequential therapy in the treatment of community-acquired pneumonia: an international, randomized, open-label study. J Chemother 2005, 17(6):636-642.

[43] Kolditz M, Halank M, Hoffken G: Short-course antimicrobial therapy for community-acquired pneumonia. Treat Respir Med 2005, 4(4):231-239.

[44] Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al: Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007, 44 Suppl 2:S27-72.

[45] Memish ZA, Shibl AM, Ahmed QA: Guidelines for the management of community-acquired pneumonia in Saudi Arabia: a model for the Middle East region. Int J Antimicrob Agents 2002, 20 Suppl 1:S1-12.

[46] Swainston Harrison T, Keam SJ: Azithromycin extended release: a review of its use in the treatment of acute bacterial sinusitis and community-acquired pneumonia in the US. Drugs 2007, 67(5):773-792.

[47] Drehobl MA, De Salvo MC, Lewis DE, Breen JD: Single-dose azithromycin microspheres vs clarithromycin extended release for the treatment of mild-to-moderate community-acquired pneumonia in adults. Chest 2005, 128(4):2230-2237.

[48] Vergis EN, Indorf A, File TM, Jr., Phillips J, Bates J, Tan J, et al: Azithromycin vs cefuroxime plus erythromycin for empirical treatment of community-acquired pneumonia in hospitalized patients: a prospective, randomized, multicenter trial. Arch Intern Med 2000, 160(9):1294-1300.

[49] Greig J, Jenks P: More on pneumonia: treatment of MRSA in community acquired pneumonia. Bmj 2006, 332(7553):1334.

[50] Bradley SF: *Staphylococcus aureus* pneumonia: emergence of MRSA in the community. Semin Respir Crit Care Med 2005, 26(6):643-649.

[51] El Solh AA, Aquilina AT, Gunen H, Ramadan F: Radiographic resolution of community-acquired bacterial pneumonia in the elderly. J Am Geriatr Soc 2004, 52(2):224-229.

[52] Janssens JP: Pneumonia in the elderly (geriatric) population. Curr Opin Pulm Med 2005, 11(3):226-230.

[53] El Solh A, Pineda L, Bouquin P, Mankowski C: Determinants of short and long term functional recovery after hospitalization for community-acquired pneumonia in the elderly: role of inflammatory markers. BMC Geriatr 2006, 6:12.

[54] Schmidt-Ioanas M, Lode H: Treatment of pneumonia in elderly patients. Expert Opin Pharmacother 2006, 7(5):499-507.

[55] Fein AM: Pneumonia in the elderly: overview of diagnostic and therapeutic approaches. Clin Infect Dis 1999, 28(4):726-729.

[56] Mandell LA, Marrie TJ, Grossman RF, Chow AW, Hyland RH: Summary of Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by the Canadian Infectious Disease Society and the Canadian Thoracic Society. Can Respir J 2000, 7(5):371-382.

[57] Mandell LA, Marrie TJ, Grossman RF, Chow AW, Hyland RH: Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by the Canadian Infectious Diseases Society and the Canadian Thoracic Society. The Canadian Community-Acquired Pneumonia Working Group. Clin Infect Dis 2000, 31(2):383-421.

[58] Marras TK, Gutierrez C, Chan CK: Applying a prediction rule to identify low-risk patients with community-acquired pneumonia. Chest 2000, 118(5):1339-1343.

[59] Bantar C, Bavestrello L, Curcio D, Jasovich A, Absi R, Bagnulo H, et al: Acute community-acquired pneumonia in adults: guidelines for initial antimicrobial therapy based on local evidence from a South American Working Group (ConsenSur). J Chemother 2002, 14, Suppl 4:1-22.

[60] Kalin M, Ortqvist A, Almela M, Aufwerber E, Dwyer R, Henriques B, et al: Prospective study of prognostic factors in

community-acquired bacteremic pneumococcal disease in 5 countries. J Infect Dis 2000, 182(3):840-847.

[61] Mortensen EM, Coley CM, Singer DE, Marrie TJ, Obrosky DS, Kapoor WN, Fine MJ: Causes of death for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study. Arch Intern Med 2002, 162(9):1059-1064.

[62] Song JH, Jung SI, Ki HK, Shin MH, Ko KS, Son JS, et al: Clinical outcomes of pneumococcal pneumonia caused by antibiotic-resistant strains in asian countries: a study by the Asian Network for Surveillance of Resistant Pathogens. Clin Infect Dis 2004, 38(11):1570-1578.

[63] Farr BM, Sloman AJ, Fisch MJ: Predicting death in patients hospitalized for community-acquired pneumonia. Ann Intern Med 1991, 115(6):428-436.

[64] Yoshimoto A, Nakamura H, Fujimura M, Nakao S: Severe community-acquired pneumonia in an intensive care unit: risk factors for mortality. Intern Med 2005, 44(7):710-716.

[65] Mohamed AR, Evans DA: The spectrum of pneumonia in 1983 at the Riyadh Armed Forces Hospital. J Infect 1987, 14(1):31-37.

[66] Alzeer A, Mashlah A, Fakim N, Al-Sugair N, Al-Hedaithy M, Al-Majed S, Jamjoom G: Tuberculosis is the commonest cause of pneumonia requiring hospitalization during Hajj (pilgrimage to Makkah). J Infect 1998, 36(3):303-306.

[67] Al-Ghamdi SM, Akbar HO, Qari YA, Fathaldin OA, Al-Rashed RS: Pattern of admission to hospitals during muslim pilgrimage (Hajj). Saudi Med J 2003, 24(10):1073-1076.

[68] Avnon LS, Jotkowitz A, Smoliakov A, Flusser D, Heimer D: Can the routine use of fluoroquinolones for community-acquired pneumonia delay the diagnosis of tuberculosis? A salutary case of diagnostic delay in a pilgrim returning from Mecca. Eur J Intern Med 2006, 17(6):444-446.

[69] Ahmed QA, Arabi YM, Memish ZA: Health risks at the Hajj. Lancet 2006, 367(9515):1008-1015.

[70] Al-Shehry AM, Al-Khan AA: Pre-Hajj health related advice, Makkah. Saudi Epidemiol Bull 1999, 6(4):29-31.

[71] Spaude KA, Abrutyn E, Kirchner C, Kim A, Daley J, Fisman DN: Influenza vaccination and risk of mortality among adults hospitalized with community-acquired pneumonia. Arch Intern Med 2007, 167(1):53-59.

[72] Alfageme I, Vazquez R, Reyes N, Munoz J, Fernandez A, Hernandez M, et al: Clinical efficacy of anti-pneumococcal vaccination in patients with COPD. Thorax 2006, 61(3):189-195.

[73] Fisman DN, Abrutyn E, Spaude KA, Kim A, Kirchner C, Daley J: Prior pneumococcal vaccination is associated with reduced death, complications, and length of stay among hospitalized adults with community-acquired pneumonia. Clin Infect Dis 2006, 42(8):1093-1101.

[74] Vila-Corcoles A, Ochoa-Gondar O, Hospital I, Ansa X, Vilanova A, Rodriguez T, Llor C: Protective effects of the 23-valent pneumococcal polysaccharide vaccine in the elderly population: the EVAN-65 study. Clin Infect Dis 2006, 43(7):860-868.

[75] Sisk JE, Moskowitz AJ, Whang W, Lin JD, Fedson DS, McBean AM, Plouffe JF, Cetron MS, Butler JC: Cost-effectiveness of vaccination against pneumococcal bacteremia among elderly people. Jama 1997, 278(16):1333-1339.

[76] Sisk JE, Whang W, Butler JC, Sneller VP, Whitney CG: Cost-effectiveness of vaccination against invasive pneumococcal disease among people 50 through 64 years of age: role of comorbid conditions and race. Ann Intern Med 2003, 138(12):960-968.

[77] Frayha HH, Al Mazrou YY: Vaccination against invasive pneumococcal disease in Saudi Arabia: where do we stand? Ann Saudi Med 2005, 25(2):90-93.

[78] Memish ZA, Balkhy HH, Shibl AM, Barrozo CP, Gray GC: *Streptococcus pneumoniae* in Saudi Arabia: antibiotic resistance and serotypes of recent clinical isolates. Int J Antimicrob Agents 2004, 23(1):32-38.

[79] Ahmed K, Martinez G, Wilson S, Yoshida R, Dhar R, Mokaddas E, et al: The prevalence and clonal diversity of penicillin-resistant *Streptococcus pneumoniae* in Kuwait. Epidemiol Infect 2000, 125(3):573-581.

[80] Adhami N, Arabi Y, Raees A, Al-Shimemeri A, Ur-Rahman M, Memish ZA: Effect of corticosteroids on adult varicella pneumonia: cohort study and literature review. Respirology 2006, 11(4):437-441.

[81] Abba AA, Al-Khuwaitir TS, Al-Moghairi AM, Garg H: Presentation and outcome of varicella pneumonia in adults. Saudi Med J 2005, 26(2):338-340.

[82] Ahmed R, Ahmed QA, Adhami NA, Memish ZA: Varicella pneumonia: another 'steroid responsive' pneumonia? J Chemother 2002, 14(2):220-222.

[83] Almuneef M, Dillon J, Abbas MF, Memish Z: Varicella zoster virus immunity in multinational health care workers of a Saudi Arabian hospital. Am J Infect Control 2003, 31(6):375-381.

[84] Almuneef M, Memish ZA, Abbas ME, Balkhy HH: Screening healthcare workers for varicella-zoster virus: can we trust the history? Infect Control Hosp Epidemiol 2004, 25(7):595-598.

[85] Almuneef M, Memish ZA, Balkhy HH, Alotaibi B, Helmy M: Chickenpox complications in Saudi Arabia: Is it time for routine varicella vaccination? Int J Infect Dis 2006, 10(2):156-161.

[86] Almuneef MA, Memish ZA, Balkhy HH, Otaibi B, Helmi M: Seroprevalence survey of varicella, measles, rubella, and hepatitis A and B viruses in a multinational healthcare workforce in Saudi Arabia. Infect Control Hosp Epidemiol 2006, 27(11):1178-1183.

[87] Memish ZA, Oni GA, Bannatyne RM, Qasem L: The cost-saving potential of prevaccination antibody tests when implementing a mass immunization program. Mil Med 2001, 166(1):11-13.

[88] Smith NM, Bresee JS, Shay DK, Uyeki TM, Cox NJ, Strikas RA: Prevention and Control of Influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2006, 55(RR-10):1-42.

[89] Gatrad AR, Shafi S, Memish ZA, Sheikh A: Hajj and the risk of influenza. Bmj 2006, 333(7580):1182-1183.

[90] Rashid H, Shafi S, Bashir HE, Haworth E, Memish ZA, Ali KA, Booy R: Influenza and the Hajj: defining influenza-like illness clinically. Int J Infect Dis 2007. May 29: Epub ahead of print.

[91] Shafi S, Rashid H, Ali K, El Bashir H, Haworth E, Memish ZA, Booy R: Influenza vaccine uptake among British Muslims attending Hajj, 2005 and 2006. Bmj 2006, 333(7580):1220.

[92] Granich R, Binkin N, Jarvis W, Simone P, Rieder H, Espinal M, Kumaresan J: World Health Organization guidelines for prevention of tuberculosis in healthcare facilities in countries with limited resources World Health Organization 1999:1-50.

[93] Jensen PA, Lambert LA, Iademarco MF, Ridzon R: Guidelines for preventing the transmission of Mycobacterium tuberculosis in health-care settings, 2005. MMWR Recomm Rep 2005, 54(17):1-141.

[94] Ramirez J: Multicenter, multinational observational studies: a new approach to studying community-acquired pneumonia. Respir Care Clin N Am 2005, 11(1):35-44.

Journal of Chemotherapy

INDEXED IN: MEDLINE (INDEX MEDICUS), CURRENT CONTENTS/CLINICAL PRACTICE ®, RESEARCH ALERT DIRECT ®, CHEMICAL ABSTRACTS, EMBASE/EXCERPTA MEDICA, BIOSIS AND IS AVAILABLE ON ADONIS CD-ROM. SEE OUR HOMEPAGE ON THE WORLD WIDE WEB FOR BIBLIOGRAPHIC SEARCH: WWW.JCHEMOTHER.IT

The Journal of Chemotherapy publishes peer-reviewed experimental and clinical research articles, reviews and letters concerning antimicrobial, anticancer and immunomodulating chemotherapy. The acceptance of submitted manuscripts will be determined by the editors and referees expert in their field.

Instructions to authors for preparation of manuscripts

1. The manuscript may be **submitted by post to Journal of Chemotherapy,** Department of Pharmacology, Viale Pieraccini 6 - 50139 Firenze, Italy or electronically by **e-mail attachment** to info@jchemother.it.

2. The author's **letter accompanying** the manuscript must state that the manuscript has not been submitted for publication elsewhere. After publication the **copyright** of the article transfers to the Journal of Chemotherapy.

3. Authors are responsible for **obtaining permission** from other copyright holders to reproduce any materials such as tables or figures which have already been published elsewhere. The copyrighted table or figure must contain in a footnote the source of the item and «with permission».

4. The manuscript must be written in **English**. Submit 3 printed-out copies plus one copy on computer disk (by post) or one electronic copy sent by e-mail to info@jchemother.it. The electronic copy **must be single-spaced. Number all pages and lines of text.**

5. **Experimental and clinical research papers**, in most cases, should adhere to the following **format:** Title page, Summary, Introduction, Materials and Methods or Patients and Methods, Results, Discussion, Acknowledgements, References, Figure legends, Tables, Figures.

Reviews should always include a brief Summary and subsequent subheadings are at the author's discretion. **Letters** should not have a Summary, but be a brief explanation of the problem, methods, results and conclusion. One or two tables and figures may be submitted with a Letter.

6. The **title page** must contain:

(a) a concise but informative title;

(b) names of all authors and their affiliating institutions indicated by numerical footnotes;

(c) name, address, telephone, fax numbers and e-mail address of the author to whom correspondence is to be addressed.

7. The **summary** should be no more than 150 words. Provide 3-10 **key words** for indexing your article.

8. The **introduction** should state the background and purpose of the topic. Cite only those references which are strictly pertinent.

9. The **materials and methods** or **patients and methods** section should describe materials or your subjects as well as the methods sufficiently in detail to allow other researchers to reproduce your study.

10. The **results** which are presented in tabular or illustrative form should not be reiterated in the text, but only the most salient findings should be emphasized.

11. The **discussion** should relate the relevance of the study's results to other data from the literature.

12. Grants or funding of the research from pharmaceutical firms must be stated in the **Acknowledgements.** Authors may also acknowledge institutional funding or grants as well as technical assistance and contributions not justifying authorship.

13. Use the Vancouver style **reference system** recommended by the International Committee of Medical Journal Editors: **number references consecutively in the order in which they are mentioned in the text. Journal titles of more than one word are to be abbreviated** according to the *Index Medicus* style. Journal titles of only one word should not be abbreviated at all.

(Contd...)

(continued)

Journal of Chemotherapy

Instructions to authors for preparation of manuscripts

«Unpublished observations» and «personal communications» will not be accepted as references in the bibliography and should be inserted in the text in parentheses and the use of abstracts from meetings is discouraged.

See examples of correct forms of references below.

Journals (list all authors when six or less; when seven or more, list first six and add "et al."):

[1] Wood MJ. Chemotherapy for gram-positive nosocomial sepsis. J Chemother 1999; 11 (6): 446-452.

[2] Bazzoli F, Zagari RM, Pozzato P et al. *Helicobacter pylori*: optimum diagnosis and test of cure. J Chemother 1999; 11 (6): 601-606.

Books and other monographs

[3] Murray PR, Baron EJ, Pfaller MA, Tenover FC, Yolken RH, eds. Manual of Clinical Microbiology. 6th ed. Washington, DC: ASM Press. 1995: Preface.

[4] Herrmann JE. Immunoassays for the diagnosis of infectious diseases. In: Murray PR, Baron EJ, Pfaller MA, Tenover FC, Yolken RH, eds. Manual of Clinical Microbiology. 6th ed. Washington, DC: ASM Press. 1995: 110-122.

[5] Barie PS. Management of complicated intra-abdominal infections. In: Periti P, Tonelli F, eds. Proceedings of the Third Symposium on the Control of Surgical Infections. Florence, Italy. J Chemother 1999; 11 (6): 464-477.

[6] The European *Helicobacter pylori* Study Group: Current European concepts in the management of *Helicobacter pylori* infection. The Maastricht consensus report. Gut 1997; 41: 8-13.

14. **Tables** should be numbered consecutively with Arabic numerals. Cite each table in the text. Obtain permission to reproduce **data from another source** (published or not). Give each table a brief title. Keep tables to a minimum and always provide an electronic version.

15. **Figures** may be good laser prints or photographs. Submit the electronic version whenever possible. Label each figure with the author's name, figure number (Arabic numerals) and indicate top of figure, using an adhesive label. Do not write directly on the backs of figures. Any **photomicrographs** must have an internal scale marker (do not give magnification because printing reduction will alter it). Cite all figures in text. Color photographs require extra cost on the part of the authors. Type figure legends on a separate sheet. Keep figures to a minimum.

16. **Drugs, chemicals and equipment** should include the name of the manufacturer and city, inserted in parenthesis after the generic or international nonproprietary name.

17. **Ethics:** Any studies involving experimentation on human beings must indicate whether procedures were in accordance with the Helsinki Declaration or the Ethical Committee of the authors' institution. Patients should not be identifiable in any photographs or their written permission is required. Authors are responsible for complying with national, international or institutional guidelines on the care and use of experimental animals.

18. Describe **statistical methods** with enough detail to allow reproduction of the study by another researcher.

19. Use the **International System of Units** (**SI**) for measurements, i.e., metric units, Celsius for temperatures. Follow SI abbreviations, for example, write microgram as μg, not mcg.

20. Use **standard abbreviations.** Avoid abbreviations in the title or summary. Aside from standard units of measurements, indicate the full term the first time an abbreviation is used in the text. Do not overuse abbreviations as they impede comprehension.

21. **Provide the full Latin genus and species name (in italics)** of all microorganisms the first time they are mentioned in the text and abbreviate genus name thereafter. For example, use *Staphylococcus aureus* the first time and S. *aureus* thereafter.

22. The first set of **printer's proofs** will be sent to authors for correction and are corrected by the managing editor. Authors should keep a copy of their manuscript to use in proof correction, as this will not be sent back to them. Authors must return the corrected proofs to the managing editor within the time designated to insure that their corrections are inserted in the article. All papers are edited for English usage and for conformity to the journal's bibliographic style.

23. Authors will be sent a **reprint price sheet** and order form with the proofs. Reprints are available after publication of the article.

€ 6,92 (...)