Western Cape Government
Health

CHIEF DIRECTORATE: Emergency & Clinical Support Services
Directorate: Pharmacy Services
Reference: 18/2/18/7
Enquiries: Ms Y Johnson
Email: Yasmina.Johnson@westerncape.gov.za

CIRCULAR H169/2020

TO: DDG: CHIEF OF OPERATIONS
CHIEF DIRECTORS; DIRECTORS AND HEADS OF INSTITUTIONS
MANAGER: CAPE MEDICAL DEPOT
HEAD OF HEALTH: CITY OF CAPE TOWN

N.B. FOR CIRCULATION TO ALL MEDICAL, PARAMEDICAL, PHARMACEUTICAL AND NURSING PERSONNEL

ANTIMICROBIAL STEWARDSHIP FOR ADULT PATIENTS WITH COVID-19 IN HOSPITAL

PURPOSE AND SCOPE

The COVID-19 pandemic challenges all aspects of healthcare including recognition and management of serious acute bacterial infection and effective delivery of antimicrobial stewardship.

Principles of antimicrobial stewardship remain as relevant as before, if not more so, during the COVID-19 pandemic.

The purpose of this guideline is to ensure the best antimicrobial management of suspected or confirmed bacterial pneumonia in adults in hospital during the COVID-19 pandemic. This includes people presenting to hospital with moderate to severe community-acquired pneumonia and people who develop pneumonia while in hospital.

This rapid guideline was developed by the Provincial Antimicrobial Stewardship Committee in direct response to the evolving situation and what antimicrobials you need to stop or start during the pandemic. The recommendations are based on evidence and national guidelines.

The guideline will be reviewed and updated as the knowledge base and expert experience develops.

MS K LOWENHERZ
DIRECTOR: PHARMACY SERVICES
DATE 17/08/20

4th Floor, 16 Chiappini Street, Cape Town, 8001
Tel: +27 21 483 6198 / +27 21 483 8702
P O Box 2060, Cape Town, 8000
www.westerncape.gov.za

ANTIMICROBIAL TREATMENT for PNEUMONIA[1, 2, 5]

- **There is no specific antimicrobial treatment for COVID-19.**
- **If evidence of bacterial infection exists e.g. if chest X-ray shows dense, unilateral consolidation or is not typical of COVID-19, antibiotics for suspected pathogens may be started on presentation. This may include conventional or atypical bacterial pathogens, influenza or PJP.**
- **Ideally, blood cultures should be obtained before commencement of antimicrobials.**
- **STOP ANTIMICROBIALS IF COVID-19 CONFIRMED AND NO SUSPECTED CO-INFECTION.**

Read in conjunction with the Hospital Adult Standard Treatment Guidelines & Essential Medicines List (EML)

NON-SEVERE PNEUMONIA

Community-acquired pneumonia without features of severe pneumonia and without co-morbidity and in patients <65 years of age

- Ampicillin, IV, 1g 6 hourly.

  In haemodynamically stable patients with respiratory rate <25 breaths/min and the temperature is <37.8°C switch to:
- Amoxicillin, oral, 1g 8 hourly to complete 5 days of treatment.

Community-acquired pneumonia without features of severe pneumonia in patients >65 years of age or co-morbidity (e.g. COPD, HIV, cardiac failure, diabetes)

- Ceftriaxone, IV, 2 g daily.

  In haemodynamically stable patients with respiratory rate <25 breaths/min and the temperature is <37.8°C switch to:
- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly to complete 5 - 7days of treatment.

Severe penicillin allergy:

- Moxifloxacin, oral, 400 mg daily for 5 – 7 days.

If poor response after 48 hours, exclude TB and consider atypical bacterial pneumonia, which requires treatment with a macrolide (see below).

SEVERE PNEUMONIA

Severe pneumonia (cyanosis, confusion, hypotension or respiratory rate >30 breaths/min):

- Ceftriaxone, IV, 2 g daily:
  In haemodynamically stable patients with respiratory rate <25 breaths/min and the temperature is <37.8°C switch to:
- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly to complete 5 – 7 days of treatment.

AND

- Azithromycin, 500 mg, slow IV (over not less than 60 minutes) daily for 3 days.

Severe penicillin allergy:

- Moxifloxacin, IV, 400 mg daily.
  In haemodynamically stable patients with respiratory rate <25 breaths/min and the temperature is <37.8°C switch to:
- Moxifloxacin, oral, 400 mg daily for 5 – 7 days.

Note: There is no need to add a macrolide, as moxifloxacin has adequate cover for the atypical bacteria.

INFLUENZA

If **seasonal epidemiology fits** and the patient has **severe illness**, initiate oseltamivir 75mg.

Consult with ID specialist / microbiologist / consultant to continue treatment to complete the course of

- Oseltamivir 75mg twice a day for 10 days,

HOSPITAL ACQUIRED PNEUMONIA (HAP) is defined as a new lung infiltrate (not present on admission) plus clinical evidence that the infiltrate is an infection (e.g. new onset of fever, purulent sputum, leukocytosis) occurring >48 hours after admission to hospital. HAP has a high morbidity and mortality and early appropriate antibiotic therapy is essential. Infection may be due to multi-drug resistant organisms, particularly in patients with prior intravenous antibiotic use within 90 days.

VENTILATOR-ASSOCIATED PNEUMONIA (VAP) occurs >48 hours after intubation. VAP is more often due to multi-drug resistant organisms than HAP.

Empiric antibiotic therapy[2]

The empiric antimicrobial regimens for HAP and VAP suggested below may need to be tailored based on local hospital epidemiology. Therapy should be adjusted according to culture result. A good quality Gram stain may be useful in guiding the choice of initial therapy.

***HAP* with no prior intravenous antibiotic use within 90 days:**

- Ceftriaxone, IV, 2 g daily for 10 days

and

- **Amikacin, IV, 15 mg/kg daily(max 1,5g per day) for 10 days

Severe Penicillin allergy:

- Moxifloxacin, oral/IV, 400 mg daily for 10 days

and

- **Amikacin, IV, 15 mg/kg daily (max 1,5g per day) for 10 days

HAP* with prior intravenous antibiotic use within 90 days or *VAP

Antibiotic choice will depend on local susceptibility patterns.

Option 1 for 10 days:

- Piperacillin/tazobactam, IV, 4.5 g 8 hourly

and

- **Amikacin, IV, 15 mg/kg daily (max 1,5g per day)

Option 2 for 10 days, if option 1 is not appropriate:

- **Cefepime, IV, 2 g 12 hourly.

Option 3 for 10 days, if option 1 and 2 are not appropriate:
Carbapenem with activity against Pseudomonas:

- Imipenem/cilastan, IV, 1000/1000 mg 8 hourly (except CNS infections or known epileptics).

Option 4 for 10 days, if option 1, 2 and 3 are not appropriate

- Meropenem, IV, 2 g 8 hourly (CNS infections or known epileptics).

Note: De-escalate as soon as the culture is available.

****See Hospital Adult STG & EML Appendix II** for individual dosing and monitoring for response and toxicity.

PNEUMOCYSTIS JIROVECII (PJP)

AIDS (WHO clinical stage 4); CD4 <200 cells/mm^3 and not on cotrimoxazole for >1 month; chest infiltrates compatible with PJP on X-ray, and hypoxaemia, consider

- Cotrimoxazole, oral / IVI:
  - <60 kg 240mg/1200mg 6 hourly for 21 days
  - ≥60 kg 320mg/1600mg 6 hourly for 21 days

ANTIMICROBIAL STEWARDSHIP FOR ADULT PATIENTS WITH COVID-19 IN HOSPITAL

Suspected or confirmed Mild, Moderate or Severe COVID-19 patients:

If there is confidence that the clinical features are typical for COVID-19, it is **reasonable NOT to start empirical antibiotics**[5,6,7].

- Evidence so far suggests that bacterial co-infection occurs in less than 10% of patients with COVID-19[3,4]. Patients in critical care have an increased likelihood of bacterial infection compared with patients in other hospital wards or settings[2].
- Inappropriate antibiotic use may reduce their availability, and indiscriminate use may lead to *Clostridioides difficile* infection and antimicrobial resistance[3,4,,7].
- Empirical antibiotics should be started if there is clinical suspicion of bacterial infection, including characteristic symptoms (e.g. CURB-score) and localised chest findings; ideally with blood cultures taken first[5,6,7,].
- The differential diagnosis of suspected cases includes influenza (considering seasonal epidemiology), both conventional and atypical bacterial pneumonias, and in patients with HIV and a CD4 count <200 cells/mm3 (or equivalent immunosuppression), consider *Pneumocystis jirovecii* pneumonia (PJP)[5].
- Malaria, as the cause of an acute febrile illness (typically with headache, rigors and malaise), must always be considered in persons residing in or travelling from malaria transmission areas[5].
- Non-infectious causes of dyspnoea and/or fever should also be considered, such as pulmonary emboli, myocardial infarction, and heart failure[5].

Antimicrobial Stewardship Guidance Principles[6]

- Antibiotics do not treat viral infections. COVID-19 is a viral infection.
- Review diagnosis and management as more clinical information becomes available, ideally 24hourly.
- If there is no continued indication for an antibiotic, it should be discontinued.
- Ensure antibiotic duration is as short as possible as per guidance documents; usually 5 to 7 days; or 10 days for hospital acquired infections.
- In those receiving IV antibiotics consider IV to oral switch daily.
- Frail elderly patients are at greater risk of complication and death from all infections. Although there may be a lower threshold for prescribing antibiotics, older patients are also at greater risk of harm from antibiotics[2].
- Checklist for antimicrobial stewardship:
    - ✓ Is there an appropriate indication?
    - ✓ Have appropriate cultures been sent?
    - ✓ Antibiotic choice – preferably "Access" antibiotics as per the WHO AWaRe classification
    - ✓ Use appropriate: dose; frequency; route; duration and therapeutic drug monitoring
    - ✓ De-escalation –
        - ➢ narrowest-spectrum antibiotic that can used to treat the bacterial infection and
        - ➢ route of administration - attempts to convert early from parenteral to oral use

4th Floor, 16 Chiappini Street, Cape Town, 8001
Tel: +27 21 483 6198 / +27 21 483 8702
P O Box 2060, Cape Town, 8000
www.westerncape.gov.za

Consider the following tests to guide decisions about using antibiotics[5,6]

- For patients with severe disease who require admission, appropriate tests may include:
  - HIV test (if status unknown)
  - Full blood count + differential
  - Blood culture
  - Legionella & pneumococcal urine antigen
  - Nasopharyngeal and/or oropharyngeal swabs for detection of viral and atypical pathogens
  - Chest radiography
  - Sputum for MCS and *Mycobacterium tuberculosis* detection (GeneXpert MTB/RIF Ultra).
  - Urine for lipoarabinomannan (LAM) if HIV positive
  - Beta-D-glucan and expectorated sputum/tracheal aspirate for PJP if HIV positive and clinically suspicious of PJP (don't induce sputum though)
- A neutrophil count outside the normal range or lobar consolidation on chest imaging may suggest a bacterial infection, but their absence does not exclude it.
- High C-reactive protein levels do not necessarily indicate that the pneumonia is due to bacteria rather than COVID-19. Published data and clinical opinion suggest that many patients with COVID-19 have raised C-reactive protein levels, meaning that this does not necessarily indicate that there is a bacterial infection.
- There is insufficient evidence to recommend routine procalcitonin (PCT) testing to guide decisions about antibiotics. SARS-CoV-2 induced immune dysregulation increases production of cytokines that increase PCT. It is unclear whether PCT adds benefit beyond what is suggested in recommendations to guide decisions about antibiotics. The most appropriate threshold for procalcitonin is also uncertain.

Patients already on an antibiotic started in the community for suspected pneumonia[6]:

- Review the antibiotic choice and change the antibiotic, if appropriate.
- Give oral antibiotics if the patient can take oral medicines and their condition is not severe enough to need intravenous antibiotics.
- Seek specialist advice on antibiotic treatment for patients who:
  - are immunocompromised
  - have a history of infection with resistant organisms
  - have a history of repeated infective exacerbations of lung disease
  - are pregnant
  - are in critical care.

When a decision to start antibiotics has been made[6]:

- Start empirical antibiotic treatment as soon as possible after establishing a diagnosis of pneumonia, and preferably within 4 hours.
- Do not wait for microbiological test results.
- Start treatment within 1 hour if the patient has suspected infection and meets any of the high-risk criteria for this as outlined in Appendix A (see attached).
- Review all antibiotics at 24 to 48 hours or as soon as test results are available.
- For patients newly diagnosed with HIV, ART should be started as soon as the patient is ready.
- Ensure patients have been adequately vaccinated (e.g. against influenza).

Antimicrobial choice (See pg 2 above): Adult Hospital Level STGs and EML 2019 Edition v2.0[1]
http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults?download=3974:standard-treatment-guidelines-and-essential-medicines-list-for-south-africa

4th Floor, 16 Chiappini Street, Cape Town, 8001
Tel: +27 21 483 6198 / +27 21 483 8702
P O Box 2060, Cape Town, 8000
www.westerncape.gov.za

Assessing the ongoing need for antibiotics[5,6]

Review all antibiotics at 24 to 48 hours or as soon as test results are available.

When to stop antibiotics

Use the following signs, symptoms and test results to help inform the overall clinical assessment and decision about when to safely stop antibiotics:

- no evidence of bacterial infection in blood, urine or sputum samples
- a positive SARS-CoV2 polymerase chain reaction (PCR) assay
- fever resolved or resolving
- symptoms and blood test results (particularly lymphopenia) consistent with COVID-19 pneumonia
- chest imaging (plain X-ray, CT scan or lung ultrasound) consistent with COVID-19 pneumonia.

Be aware that the 3 patterns on CT-chest imaging consistent with COVID-19 pneumonia according to stage of illness (from symptom onset) are:

- **early** (0 to 2 days): normal or rounded ground-glass opacities
- **intermediate** (5 to 10 days): crazy-paving opacities
- **late** (more than 10 days): consolidation. Chest imaging changes are bilateral in most patients (more than 60%), with the lung periphery and lower lobes being most involved. Early ground-glass appearances may not be visible on plain chest X-rays

Follow the *NICD Clinical Management of Suspected or Confirmed COVID-19 Disease* guidelines for persons admitted to hospital with suspected COVID-19 infection. https://www.nicd.ac.za/diseases-a-z-index/covid-19/covid-19-guidelines/clinical-management-of-suspected-or-confirmed-covid-19-disease/

Continuing antibiotics

- Continue antibiotics if there is clinical or microbiological evidence of bacterial infection, regardless of SARS-CoV2 PCR test results.
- Think about continuing antibiotics if the SARS-CoV2 PCR test is positive but clinical features are not typical for COVID-19 pneumonia.

If antibiotics are continued:

Review antibiotic choice based on microbiological test results and switch to a narrower spectrum antibiotic when appropriate.

Give patients a total of 5 days treatment, and then stop unless there is a clear indication to continue.

Review intravenous antibiotic use within 48 hours and think about switching to oral antibiotics.

Reassessment and specialist advice[6]

- Reassess patients if their symptoms do not improve as expected, or worsen rapidly or significantly.
- Seek specialist advice if:
  - there is a suspicion that the patient has an infection with multidrug-resistant bacteria and may need a different antibiotic, or
  - there is clinical or microbiological evidence of infection and the patient's condition does not improve as expected after 48 to 72 hours of antibiotic treatment.

Higher risk of resistance includes symptoms or signs starting more than 5 days after hospital admission, relevant comorbidity such as severe lung disease or immunosuppression, recent use of broad-spectrum antibiotics, colonisation with multidrug-resistant bacteria, and recent contact with a health or social care setting before current admission.

Fluoroquinolones warning: Stop treatment at the first signs of a serious adverse reaction (such as tendonitis); prescribe with special caution for people over 60 years and co-administration with a corticosteroid.

4th Floor, 16 Chiappini Street, Cape Town, 8001
Tel: +27 21 483 6198 / +27 21 483 8702
P O Box 2060, Cape Town, 8000
www.westerncape.gov.za

REFERENCES

1. National Department of Health South Africa. 2019. Essential Drugs Programme. Hospital level (Adults) Standard Treatment Guidelines and Essential Medicines List. 5th ed. 2019. National Department of Health, Pretoria, Republic of South Africa. http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

2. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB et al. 2016. Management of adults with hospital-acquired and ventilator associated pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016 Sep 1;63(5):e61-e111. https://www.ncbi.nlm.nih.gov/pubmed/27418577

3. Huang C, Wang Y, Li X, Ren L, Zhao J, et al. 2020. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020; 395:497-506. DOI: 10.1016/S0140-6736(20)30183-5

4. Rawson TM, Moore LSP, Zhu N, Ranganathan N, Skolimowska K, Gilchrist M, et al. 2020. Bacterial and fungal co-infection in individuals with coronavirus: A rapid review to support COVID-19 antimicrobial prescribing. *Clin Infect Dis*. doi: 10.1093/cid/ciaa530

5. Department of Health and National Institute for Communicable Diseases. 2020. Clinical management of suspected or confirmed COVID-19 disease Version 4. www.nicd.ac.za/diseases-a-zindex/covid-19/covid-19-guidelines/

6. National Institute for Health and Care Excellence. 2020. COVID-19 rapid guideline: antibiotics for pneumonia in adults in hospital (NG173); www.nice.org.uk/guidance/ng173

7. World Health Organisation. 2020. Clinical management of COVID-19: interim guidance, 27 May 2020. www.WHO/2019-nCoV/clinical/2020.5

4th Floor, 16 Chiappini Street, Cape Town, 8001
Tel: +27 21 483 6198 / +27 21 483 8702

P O Box 2060, Cape Town, 8000
www.westerncape.gov.za

Table 1 Risk stratification tool for adults, children and young people aged 12 years and over with suspected sepsis

Category	High risk criteria	Moderate to high risk criteria	Low risk criteria
History	Objective evidence of new altered mental state	History from patient, friend or relative of new onset of altered behaviour or mental state History of acute deterioration of functional ability Impaired immune system (illness or drugs including oral steroids) Trauma, surgery or invasive procedures in the last 6 weeks	Normal behaviour
Respiratory	Raised respiratory rate: 25 breaths per minute or more New need for oxygen (40% FiO2 or more) to maintain saturation more than 92% (or more than 88% in known chronic obstructive pulmonary disease)	Raised respiratory rate: 21–24 breaths per minute	No high risk or moderate to high risk criteria met
Blood pressure	Systolic blood pressure 90 mmHg or less or systolic blood pressure more than 40 mmHg below normal	Systolic blood pressure 91–100 mmHg	No high risk or moderate to high risk criteria met
Circulation and hydration	Raised heart rate: more than 130 beats per minute Not passed urine in previous 18 hours. For catheterised patients, passed less than 0.5 ml/kg of urine per hour	Raised heart rate: 91–130 beats per minute (for pregnant women 100–130 beats per minute) or new onset arrhythmia Not passed urine in the past 12–18 hours For catheterised patients, passed 0.5–1 ml/kg of urine per hour	No high risk or moderate to high risk criteria met
Temperature		Tympanic temperature less than 36°C	
Skin	Mottled or ashen appearance Cyanosis of skin, lips or tongue Non-blanching rash of skin	Signs of potential infection, including redness, swelling or discharge at surgical site or breakdown of wound	No non-blanching rash