SOUTH AFRICAN ADULT HOSPITAL LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 16: RESPIRATORY DISORDERS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2017 -2019)

Medicine amendment recommendations, with supporting evidence and rationale are listed below. Kindly review the medicine amendments in the context of the chapter for respiratory conditions.

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED
16.1 Asthma, acute	Salbutamol, nebulisation	Amended from respiratory solution to nebulisation (allowing for either UDV or solution); directions for use amended
	Ipratropium, nebulisation	Retained
	Fenoterol, inhalation	Deleted
- mild to moderate exacerbations, if poor response to nebulised salbutamol	Prednisone, oral	Dose and duration of therapy not amended
	Prednisone, IV	Not added
- once PEF returns to 80% of predicted/ personal best after acute treatment	Salbutamol, MDI	Retained
	Inhaled corticosteroids, MDI	Added as a therapeutic class (low dose/intermittent dosing)
	Budesonide, MDI	Listed as an example of therapeutic class in the STG (low dose/intermittent dosing)
	Beclomethasone, MDI	Added for patients on protease inhibitors (low dose/intermittent dosing)
16.2 Asthma, chronic persistent	Dry powder inhalers	Not added
- for patients with infrequent asthma symptoms < twice a month: As ***reliever/rescue therapy***	Short-acting beta blockers, MDI	Retained as a therapeutic class (low dose/intermittent dosing)
	Salbutamol, MDI	Retained (intermittent dosing)
	Inhaled corticosteroids, MDI	Added as a therapeutic class (low dose/intermittent dosing)
	Budesonide, MDI	Listed as an example of therapeutic class in the STG (low dose/intermittent dosing)
	Beclomethasone, MDI	Added for patients on protease inhibitors (low dose/intermittent dosing)
- for patients with asthma symptoms ≥ twice a month	Salbutamol, MDI	Retained (intermittent dosing)
	Inhaled corticosteroids, MDI	Retained as a therapeutic class (low dose/regular dosing)
	Budesonide, MDI	Added as an example of therapeutic class in the STG (low dose/regular dosing)
	Beclomethasone, MDI	Retained for patients on protease inhibitors (low dose/regular dosing)
-for patients with asthma symptoms almost daily or waking due to asthma at least once a week	Inhaled corticosteroids, MDI	High dose ICS deleted
	Salmeterol/fluticasone, MDI	Formulation amended to 25/250 mcg
16.3 Bronchiectasis	Antimicrobial therapy	General guidance added
- Severe penicillin allergy: "stable" bronchiectasis (Empiric antibiotic therapy)	Ciprofloxacin, oral	Not added
	Moxifloxacin, oral	Deleted
	Azithromycin, oral	Added
- More severely ill patients may require hospitalisation and initiation of parenteral antibiotic therapy.	Ceftriaxone, IV	Retained
	Amoxicillin/clavulanic acid, IV	Not added
- If pseudomonas infection is suspected or confirmed on culture:	Ciprofloxacin, oral	Retained and dose amended
	Piperacillin /tazobactam, IV	Not added
	Cefepime, IV	Not added

	Azithromycin, oral	Not added for add-on therapy to beta-lactams
16.4 Chronic obstructive pulmonary disease (COPD)		
- Antibiotic therapy	Amoxicillin, oral	Retained
	Doxycycline, oral	Added
- Severe exacerbation& non-responsive to amoxicillin	Amoxicillin/clavulanic acid, oral	Retained
- Severe exacerbation & non-responsive to doxycycline (severe penicillin allergy)	Azithromycin, oral	Retained
- Chronic therapy	Steps in treatment algorithm	Amended to reflect the GOLD Grade categories.
- GRADE B (chronic therapy)	SABA, inhaler	Directions for use amended (LABA added to and not as replacement of SABA)
	LABA, inhaler	Directions for use amended (LABA added to and not as replacement of SABA); prescriber level amended
- GRADE C and D (Moderate to very severe COPD)	SABA, inhaler	Added as standard maintenance therapy (see Grade B)
	LABA, inhaler	Added as standard maintenance therapy (see Grade B); prescriber level amended
	LABA/ICS, inhaler	Retained for exacerbations; prescriber level amended
	Long-acting muscarinic antagonists e.g.: tiotropium inhaler	Not added
16.6 Pneumonia, community acquired (CAP)		
- Diagnosis	Initial diagnostic chest x-ray	Amended – added management of patients with negative CXR
	Follow-up chest x-ray	Amended – criteria added
- Empiric antibiotic therapy	Duration of empiric antibiotic therapy	Amended
- Community-acquired pneumonia without features of severe pneumonia (Severe penicillin allergy)	Moxifloxacin, IV	Added
	Moxifloxacin, oral	Retained
- Patients > 65 years or co-morbid disease (including HIV infection)	Ceftriaxone, IV	Retained
	Amoxicillin/clavulanic acid, IV	Not added
- Severe pneumonia (cyanosis, confusion, hypotension or respiratory rate>30 breaths/min)	Ceftriaxone, IV	Retained
	Amoxicillin/clavulanic acid, IV	Not added
	Azithromycin, IV	Direction for use amended
16.11.1 INH monoresistant TB	Levofloxacin, oral	Added
	Rifampicin, oral	Retained
	Ethambutol, oral	Retained
	Pyrazinamide, oral	Retained
	Isoniazid, oral (high-dose)	Not added
16.11.2 Multidrug-resistant TB		
- injectable regimen	Kanamycin, injection	Deleted
	Moxifloxacin, oral	Deleted
	Ethionamide, oral	Deleted
	Terizidone, oral	Deleted
	Pyrazinamide, oral	Deleted
- non-injectable regimen	Clofazimine, oral	Added, with conditions
	Linezolid, oral	Added, with conditions
	Bedaquiline, oral	Added, with conditions
	Delaminid, oral	Added, with conditions
	Isoniazid, oral (high-dose)	Added, with conditions
	Levofloxacin, oral	Added, with conditions
	Ethambutol, oral	Added, with conditions
	Pyrazinamide, oral	Added, with conditions
-obsolete medicine (in surplus at pharmaceutical stores)	Kanamycin, IV	No other indication recommended
- pending DR-TB medicine	Pretomanid	Scoping review done

Latent tuberculosis infection (LTBI)		
- Isoniazid monotherapy	Isoniazid, oral	Retained, duration of therapy and indication(s) amended
- Rifapentine-isoniazid therapy (3HP monthly regimen)	Rifapentine, oral	Not added (as 3HP)
	Isoniazid, oral	Not added (as 3HP)

16.1 ASTHMA, ACUTE

Salbutamol, nebulisation: *amended from respiratory solution to nebulisation (allowing for either UDV or solution); directions for use amended*
Ipratropium, nebulisation: *retained*

Salbutamol+ ipratropium nebulisation: Recent 2017 Cochrane review shows a moderate benefit of combination (short-acting beta agonist, SABA + short-acting anticholinergic, SAAC) inhalation therapy over SABA alone in reducing hospitalisation and improving PEF in adults with acute asthma; moreso in patients with severe exacerbations.

- *Evidence:* Systematic review of 23 RCTs (n=2724) - RCTs had either high or uncertain risk of publication bias.
  - Overall, participants receiving combination inhaled therapy were less likely to be hospitalised: RR 0.72, 95% CI 0.59 to 0.87; n= 2120; 16 RCTs; I^2 = 12%; NNT=166; moderate quality of evidence.
  - Participants receiving combination inhaled therapy were more likely to experience adverse events than those treated with SABA agents alone: OR 2.03, 95% CI 1.28 to 3.20; ns = 1392; 11 RCTs; I^2 = 14%; moderate quality of evidence.

Recommendation: For severe acute asthma in adults, combination inhalation therapy (salbutamol + ipratropium) be recommended.
Rationale: Systematic review of moderate to low quality RCTs shows that combination inhalation therapy (SABA + SAAC) reduces hospitalisation and improves PEF. In particular, combination therapy was more effective in preventing hospitalisation in severe asthma cases where there is an increased risk of hospitalisation compared to mild-moderate exacerbations.
Level of Evidence: II Systematic review of RCTs of low to moderate quality

The text of the STG was amended as follows:

~~Continuous nebulisation is preferable to intermittent nebulisation with β_2-agonists for the 1st hour of therapy.~~
- ~~Salbutamol 5 mg (1 mL 0.5% respiratory solution with 4 mL sodium chloride 0.9%).~~
  - ~~Nebulise continuously (refill the nebuliser reservoir every 20 minutes) at a flow rate of 6–8 L/minute until PEF > 60% of predicted/personal best.~~
  - ~~If response to nebulised salbutamol is poor, add ipratropium bromide 0.5 mg with the 1st and subsequent refills of the nebuliser reservoir.~~
  - ~~Once a patient reaches 60% of their predicted/personal best PEF, repeat salbutamol 5 mg or fenoterol 1.25–2.5 mg 4 hourly.~~
    ~~**Note**: Fenoterol should not be used for continuous nebulisation, as a maximum safe dose in this setting has not been established.~~
- Salbutamol, nebulisation, 5 mg via nebulisation.
  - Initially nebulise continuously (refill the nebuliser reservoir every 20 minutes) at a flow rate of 6–8 L/minute until PEF >60% of predicted or >60% of personal best (see PEF charts on on pg lxxvi)).

Once patient reaches 60% of their predicted/personal best PEF, repeat salbutamol 5 mg 4 hourly.

Severe exacerbations:
ADD
- Ipratropium bromide 0.5 mg.
  - Combination salbutamol/ipratropium UDV, 5/0.5 mg preferred.

Mild to moderate exacerbations, if response to nebulised salbutamol is poor:
ADD
- Ipratropium bromide 0.5 mg with the 1st and subsequent refills of the nebuliser reservoir.

Fenoterol, inhalation: *deleted*

Salbutamol inhalation preferred as it causes less hypokalaemia and QT prolongation, and has literature supporting its use as a continuous nebulisation in acute asthma[1]. Fenoterol has a greater effect on hypokalaemia and heart rate than salbutamol.[2] [3]

Evidence:

- Cochrane review of 8 RCTs (n=461)[4]
  - Hospital admission was reduced with CBA vs intermittent beta-agonists: RR: 0.68; 95% CI: 0.5 to 0.9;
  - Patients with severe airway obstruction at presentation appeared to benefit most: RR: 0.64; 0.5 to 0.9.
  - Continuous treatment was generally well tolerated, with no clinically important differences observed in pulse rate: WMD: -2.87; -6.0 to 0.3; or blood pressure: WMD: -1.75; -5.6 to 2.1. Tremor was equally common in both groups: OR: 0.81; 0.5 to 1.3 and potassium concentration was unchanged: WMD: 0.02; -0.2 to 0.2.

Recommendation: SABA, fenoterol inhalation be removed from the STG for acute asthma in adults.

Rationale: Continuous beta-agonist (CBA) via nebulisation in the emergency setting offers additional benefits in acute asthma. However, fenoterol is associated with a greater effect on hypokalaemia and heart rate than salbutamol. (The ideal would be having a single short acting beta agonist available as a unit dose vial).

Level of Evidence: I Systematic review, III Dose response studies

The text of the STG was amended as follows:

- Once a patient reaches 60% of their predicted/personal best PEF, repeat salbutamol 5mg ~~or fenoterol 1.25–2.5mg~~ 4 hourly**.**

~~**Note**: Fenoterol should not be used for continuous nebulisation, as a maximum safe dose in this setting has not been established.~~

Mild to moderate exacerbations, if response to nebulised salbutamol is poor

Prednisone, oral**:** *dose not amended; duration of therapy not amended*

Dose: Global Initiative for Asthma Guidelines (GINA), 2019 recommends an oral prednisone dose in adults of 1mg/kg/day to maximum dose of 50 mg. The dose in the STG, 40 mg, is the middle of the usual recommended range of 30-50 mg.

Duration of therapy: External comment received to align treatment course of oral prednisone to that of COPD (5-days duration). However, South African Asthma guidelines, 2013 recommends 7-14 days and GINA 2019 Guidelines recommends 5-7 days; whilst GOLD 2018 COPD guidelines recommend prednisone for "not more than 5-7 days" for COPD exacerbations.

Recommendation: Dose retained as 40 mg; duration of prednisone, oral retained as 7 days, aligned with local and international Guidelines.

Level of Evidence: III Guidelines[5]

Prednisone, IV: *not added*

An external comment was received motivating for initial IV dose of prednisione, as gastric atony was reported to commonly occur. However, no available evidence could be sourced in the published literature for the local incidence/ prevalence rate of gastric atony in asthma patients.

Level of Evidence: III Expert opinion

[1] Camargo CA Jr, Spooner CH, Rowe BH. Continuous versus intermittent beta-agonists in the treatment of acute asthma. Cochrane Database Syst Rev. 2003;(4):CD001115. https://www.ncbi.nlm.nih.gov/pubmed/14583926

[2] Beasley R. A historical perspective of the New Zealand asthma mortality epidemics. J Allergy Clin Immunol. 2006 Jan;117(1):225-8. https://www.ncbi.nlm.nih.gov/pubmed/16429618

[3] Clark DJ, Lipworth BJ. Dose-response of inhaled drugs in asthma. An update. Clin Pharmacokinet. 1997 Jan;32(1):58-74. https://www.ncbi.nlm.nih.gov/pubmed/9012556

[4] Camargo CA Jr, Spooner CH, Rowe BH. Continuous versus intermittent beta-agonists in the treatment of acute asthma. Cochrane Database Syst Rev. 2003;(4):CD001115. https://www.ncbi.nlm.nih.gov/pubmed/14583926

[5] Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. http://www.ginasthma.org/

Reliever/rescue therapy (once PEF returns to 80% of predicted/ personal best after acute treatment)
Salbutamol, MDI: *retained*
Inhaled corticosteroids, MDI: *added as a therapeutic class (low dose –intermittent dosing)*
Budesonide, MDI: *listed as an example of therapeutic class in the STG (low dose –intermittent dosing)*
Beclomethasone, MDI: *added for patients on protease inhibitors (low dose –intermittent dosing)*

SABA with low dose ICS as rescue therapy: Aligned with GINA 2019 recommendations[6] of symptom-driven SABA together with low dose ICS; rather than SABA only as reliever therapy.

- *SABA* safety concerns were considered (β-receptor downregulation, decreased broncho-protection, rebound hyper-responsiveness, decreased bronchodilator response[7], increased allergic response and eosinophilic airway inflammation[8]. Higher use of SABA is also associated with higher risk of emergency department presentations[9] and higher mortality risk[10]). There is a lack of RCT evidence for SABA-only treatment for mild/intermittent asthma.
- *ICS* added as evidence from RCTs and observational studies suggests that low dose ICS reduces risks of severe exacerbations[11] [12], hospitalisations[13] and death[14]. Prevention of exacerbations and death was valued more highly than symptom control.

ICS+SABA: RCT[15] showed a greater reduction of exacerbations in groups receiving ICS+ SABA, as needed and regular ICS *vs* the group using as needed SABA, difference =17.80 %, p=0.002 and 17.80%, p=0.005, respectively. Kaplan–Meier analysis, below, shows that the time to first exacerbation was shortest in the as-needed SABA only group.

[6] Reddel HK, FitzGerald JM, Bateman ED, Bacharier LB, Becker A, Brusselle G, Buhl R, Cruz AA, Fleming L, Inoue H, Ko FW, Krishnan JA, Levy ML, Lin J, Pedersen SE, Sheikh A, Yorgancioglu A, Boulet LP. GINA 2019: a fundamental change in asthma management: Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. Eur Respir J. 2019 Jun 27;53(6). https://www.ncbi.nlm.nih.gov/pubmed/31249014
[7]Hancox RJ, Cowan JO, Flannery EM, Herbison GP, McLachlan CR, Taylor DR. Bronchodilator tolerance and rebound bronchoconstriction during regular inhaled beta-agonist treatment. Respir Med 2000;94:767-71. https://www.ncbi.nlm.nih.gov/pubmed/10955752
[8] Aldridge RE, Hancox RJ, Robin Taylor D, Cowan JO, Winn MC, Frampton CM, Town GI. Effects of terbutaline and budesonide on sputum cells and bronchial hyperresponsiveness in asthma. Am J Respir Crit Care Med 2000;161:1459-64. https://www.ncbi.nlm.nih.gov/pubmed/10806139
[9] Stanford RH, Shah MB, D'Souza AO, Dhamane AD, Schatz M. Short-acting β-agonist use and its ability to predict future asthma-related outcomes. Annals of Allergy, Asthma & Immunology 2012;109:403-7. https://www.ncbi.nlm.nih.gov/pubmed/23176877
[10] Suissa S, Ernst P, Boivin JF, Horwitz RI, Habbick B, Cockroft D, Blais L, et al. A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. Am J Respir Crit Care Med 1994;149:604-10. https://www.ncbi.nlm.nih.gov/pubmed/8118625
[11] Reddel HK, Busse WW, Pedersen S, Tan WC, Chen YZ, Jorup C, Lythgoe D, O'Byrne PM. Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study. Lancet. 2017 Jan 14;389(10065):157-166. https://www.ncbi.nlm.nih.gov/pubmed/27912982
[12] Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV, Ullman A, Lamm CJ, O'Byrne PM; START Investigators Group. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. Lancet. 2003 Mar 29;361(9363):1071-6. https://www.ncbi.nlm.nih.gov/pubmed/12672309
[13] Suissa S, Ernst P, Kezouh A. Regular use of inhaled corticosteroids and the long term prevention of hospitalisation for asthma. Thorax. 2002 Oct;57(10):880-4. https://www.ncbi.nlm.nih.gov/pubmed/12324675
[14] Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med. 2000 Aug 3;343(5):332-6. https://www.ncbi.nlm.nih.gov/pubmed/10922423
[15] Papi A, Canonica GW, Maestrelli P, Paggiaro P, Olivieri D, Pozzi E, Crimi N, Vignola AM, Morelli P, Nicolini G, Fabbri LM; BEST Study Group. Rescue use of beclomethasone and albuterol in a single inhaler for mild asthma. N Engl J Med. 2007 May 17;356(20):2040-52. https://www.ncbi.nlm.nih.gov/pubmed/17507703

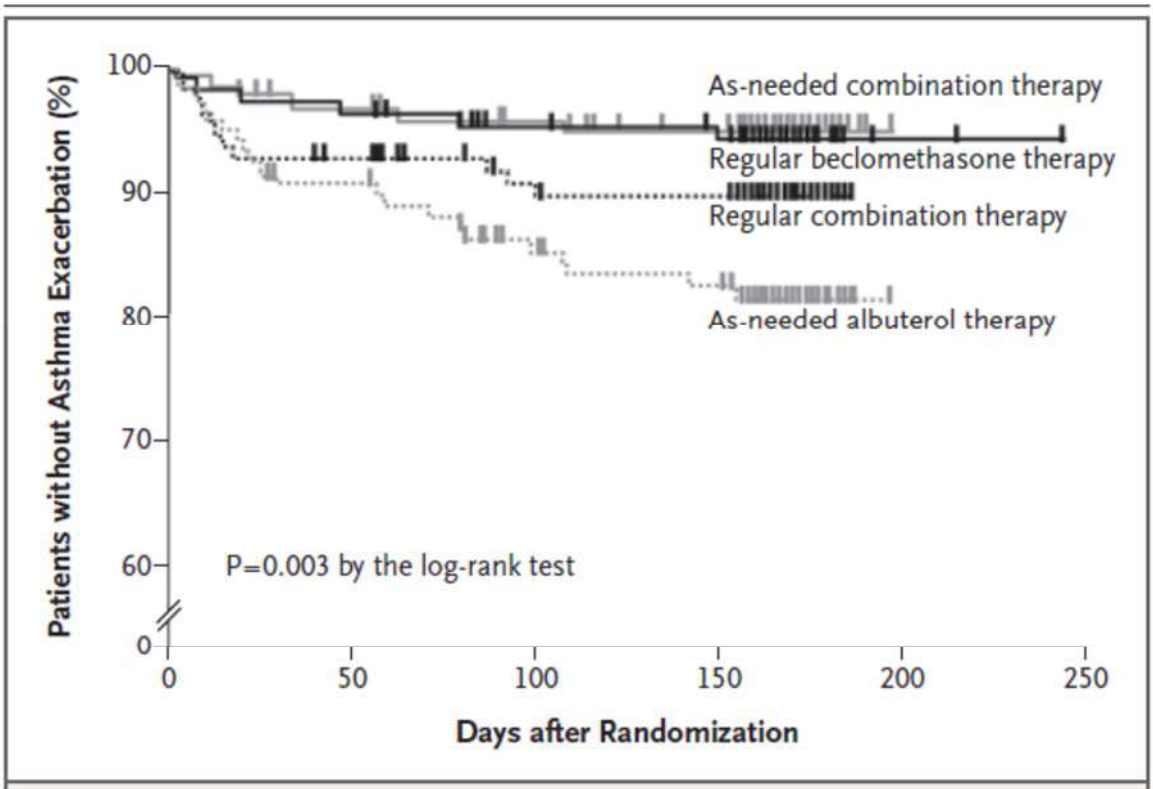

Figure 4. Kaplan–Meier Estimates of the Time to First Asthma Exacerbation in the Modified Intention-to-Treat Population.

Tick marks represent a first asthma exacerbation. As-needed combination therapy consisted of placebo twice daily plus 250 μg of beclomethasone and 100 μg of albuterol in a single inhaler as needed; as-needed albuterol therapy, placebo twice daily plus 100 μg of albuterol as needed; regular beclomethasone therapy, 250 μg of beclomethasone twice daily and 100 μg of albuterol as needed; and regular combination therapy, 250 μg of beclomethasone and 100 μg of albuterol in a single inhaler twice daily plus 100 μg of albuterol as needed.

Budesonide listed as example of ICS class in the STG, based on price
Price: Comparative cost per day is as follows:

- Budesonide 200 mcg 12 hourly is R0.36[16]
- Beclomethasone 200 mcg12 hourly = R 0.56[17]

(Note: the other therapeutic alternatives to be added to the therapeutic interchange database).

Protease inhibitors interaction with ICS: The Primary Health Care STGs and EML, 2018 edition - respiratory chapter recommends that patients on protease inhibitors (PI) requiring inhaled corticosteroids be referred to higher level of care for management. There is significant drug interaction of budesonide/ fluticasone/ mometasone with PIs, which may result in iatrogenic Cushing's syndrome. PIs do not interact with beclomethasone, so that is the best ICS to use in patients on PIs.

[16] Contract circular HP07-2017DAI: Budesonide 200 mcg, 300 doses =R 53.30.
[17] Contract circular HP07-2017DAI: Beclomethasone 200 mcg, 200 doses = R56.36

Previously, NEMLC[18] considered that it was practical to stock beclomethasone in addition to budesonide at all PHC clinics, as patients on PIs who require ICS are relatively uncommon. These patients are recommended to be referred to secondary level of care to initiate beclomethasone. For chronic patients beclomethasone could be accessed at primary level of care through down-referral mechanisms.

Level of Evidence III Case reports[19] [20] [21] [22]

16.2 ASTHMA, CHRONIC PERSISTENT

For patients with infrequent asthma symptoms < twice a month:

Reliever/rescue therapy:

Salbutamol, MDI: *retained (intermittent dosing)*
Inhaled corticosteroids, MDI: *added as a therapeutic class (low dose – intermittent dosing)*
Budesonide, MDI: *listed as an example of therapeutic class in the STG (low dose – intermittent dosing)*
Beclomethasone, MDI: *added for patients on protease inhibitors (low dose – intermittent dosing)*
Management for mild intermittent aligned to management in section 16.1: Asthma acute and GINA 2019 guidance[23].

For patients with asthma symptoms ≥ twice a month

Salbutamol, MDI: *retained (intermittent dosing)*
Inhaled corticosteroids, MDI: *retained as a therapeutic class (low dose – regular dosing)*
Budesonide, MDI: *retained as an example of therapeutic class in the STG (low dose – regular dosing)*
Beclomethasone, MDI: *retained for patients on protease inhibitors (low dose – regular dosing)*
Aligned with GINA 2019 guidance, [24] which remains unchanged. Evidence supports low dose ICS in reducing severe exacerbations[25] [26], hospitalizations[27] and death[28]; with serious exacerbations decreasing by 31% in study participants with 0-1 symptom days per week[29], with regular low-dose ICS compared to placebo.

[18] Minutes of the NEMLC meeting of 12 April 2018.
[19] Kedem E, Shahar E, Hassoun G, Pollack S. Iatrogenic Cushing's syndrome due to coadministration of ritonavir and inhaled budesonide in an asthmatic human immunodeficiency virus infected patient. J Asthma. 2010 Sep;47(7):830-1. https://www.ncbi.nlm.nih.gov/pubmed/20653496
[20] Blondin MC, Beauregard H, Serri O. Iatrogenic Cushing syndrome in patients receiving inhaled budesonide and itraconazole or ritonavir: two cases and literature review. Endocr Pract. 2013 Nov-Dec;19(6):e138-41. https://www.ncbi.nlm.nih.gov/pubmed/23807527
[21] Frankel JK, Packer CD. Cushing's syndrome due to antiretroviral-budesonide interaction. Ann Pharmacother. 2011 Jun;45(6):823-4. https://www.ncbi.nlm.nih.gov/pubmed/21558486
[22] Yoganathan K, David L, Williams C, Jones K. Cushing's syndrome with adrenal suppression induced by inhaled budesonide due to a ritonavir drug interaction in a woman with HIV infection. Int J STD AIDS. 2012 Jul;23(7):520-1. https://www.ncbi.nlm.nih.gov/pubmed/22844010
[23] Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. http://www.ginasthma.org/
[24] Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. http://www.ginasthma.org/
[25] Reddel HK, Busse WW, Pedersen S, Tan WC, Chen YZ, Jorup C, Lythgoe D, O'Byrne PM. Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study. Lancet. 2017 Jan 14;389(10065):157-166. https://www.ncbi.nlm.nih.gov/pubmed/27912982
[26] Pauwels RA, Pedersen S, Busse WW, Tan WC, Chen YZ, Ohlsson SV, Ullman A, Lamm CJ, O'Byrne PM; START Investigators Group. Early intervention with budesonide in mild persistent asthma: a randomised, double-blind trial. Lancet. 2003 Mar 29;361(9363):1071-6. https://www.ncbi.nlm.nih.gov/pubmed/12672309
[27] Suissa S, Ernst P, Kezouh A. Regular use of inhaled corticosteroids and the long term prevention of hospitalisation for asthma. Thorax. 2002 Oct;57(10):880-4. https://www.ncbi.nlm.nih.gov/pubmed/12324675
[28] Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. N Engl J Med. 2000 Aug 3;343(5):332-6. https://www.ncbi.nlm.nih.gov/pubmed/10922423
[29] Reddel HK, Busse WW, Pedersen S, Tan WC, Chen YZ, Jorup C, Lythgoe D, O'Byrne PM. Should recommendations about starting inhaled corticosteroid treatment for mild asthma be based on symptom frequency: a post-hoc efficacy analysis of the START study. Lancet. 2017 Jan 14;389(10065):157-166. https://www.ncbi.nlm.nih.gov/pubmed/27912982

For patients with asthma symptoms almost daily or waking due to asthma at least once a week:
Inhaled corticosteroid: *step up therapy – doubling of ICS dose – deleted*
LABA/ICS: *added as step up therapy*
Salmeterol/fluticasone 50/500 mcg, inhaler: *added as example of class of LABA/ICS (high dose)*
Salmeterol/fluticasone 50/250 mcg, inhaler: *added as example of class of LABA/ICS (low dose)*

Evidence for ICS/LABA: A Cochrane review (Ducharme 2010)[30] showed a modest decreased risk of exacerbation requiring systemic corticosteroids in ICS/LABA versus increased dose ICS in patients uncontrolled on low to moderate doses of ICS; NNT= 73 (95% CI 42 to 437).
Rationale: Systematic review showed that ICS/LABA had a modest decreased risk of exacerbation requiring systemic corticosteroids vs high dose ICS in adults uncontrolled on low-moderate dose ICS.
Level of Evidence: I Systematic review

Salmeterol/fluticasone, MDI, low dose: External comment received to consider 25/250 formulation as opposed to 50/500 mcg formulation to allow for more flexibility with dosing. In accordance with step 3 of 2019 GINA guidance, low dose ICS with LABA. As standard dose of salmeterol in adults is 50 mcg 12 hourly, 50/250 mcg formulation has been recommended.
Level of Evidence: III Guidelines[31] [32], Expert opinion

16.3 BRONCHIECTASIS

Antimicrobial therapy: *general guidance added*
Following text added to STG:

Antibiotic therapy in patients with bronchiectasis should only be used when there is either systemic evidence of sepsis such as pyrexia or increasing sputum purulence or volume. Antibiotic choices should be guided by sputum microscopy, culture and sensitivity. It is critical that the first approach should be to increase the number and duration of home physiotherapy sessions.

Severe penicillin allergy: "stable" bronchiectasis
Empiric antibiotic therapy
Ciprofloxacin, oral: *not added*
Moxifloxacin, oral: *not added*
Azithromycin, oral: *added*

Most antibiotic recommendations for non-cystic fibrosis bronchiectasis are extrapolated from RCTs done in cystic fibrosis. Empiric therapy for "stable" bronchiectasis covers suspected pathogens *Haemophilus influenzae* and *Streptococci.* Macrolides are recommended by most guidelines, and NEMLC considered that azithromycin was sufficient as empiric therapy in penicillin allergic patients that are stable; where *Pseudomonas aeruginosa* has not been confirmed. Fluoroquinolones should be restricted for exacerbations due to resistant organisms (Moxifloxacin active against *Haemophilus influenzae* and *Streptococci,* as well as *Moraxella catarrhalis*, *Staphylococcus* aureus and *Enterobacteriaceae).* Severe infection is associated with *Pseudomonas aeruginosa,* and the STG algorithm does recommend that where pseudomonas is suspected, add ciprofloxacin. Cases non-responsive to empiric therapy require sputum M, C&S testing. Ciprofloxacin does not cover *Streptococci.*
Recommendation: Empiric therapy in non-severe penicillin allergic bronchiectasis cases be amended to azithromycin.

[30] Ducharme FM, Ni Chroinin M, Greenstone I, Lasserson TJ. Addition of long-acting beta2-agonists to inhaled steroids versus higher dose inhaled steroids in adults and children with persistent asthma. Cochrane Database Syst Rev. 2010 Apr 14;(4):CD005533. https://www.ncbi.nlm.nih.gov/pubmed/20393943
[31] Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2019. http://www.ginasthma.org/
[32] SAMF, 2106

Rationale: Suspected pathogens in non-severe cases are mostly *Haemophilus influenzae* and *Streptococci.* Azithromycin provides cover for *Haemophilus influenzae* and *Streptococci;* but the STG does indicate that where pseudomonas is suspected, add ciprofloxacin. The local prevalence of pseudomonas in bronciectasis is currently unknown. Ciprofloxacin does not cover *Streptococci.*
Level of Evidence: III Local susceptibility data

More severely ill patients may require hospitalisation and initiation of parenteral antibiotic therapy.
Ceftriaxone, IV: *retained*
Amoxicillin/clavulanic acid, IV: *not added*

Background: An external comment was received motivating for the use of amoxicillin/clavulanic acid, IV, as ceftriaxone, IV does not cover any of the important pathogens and causes considerable collateral damage (driving ESBL mutations).

Pathogens assumed to be similar to those in community acquired pneumonia, covered by ceftriaxone (and recommended in the British Thoracic Society Guidelines[33]). Co-amoxyclav acknowledged as a work horse antibiotic, but is more expensive than ceftriaxone. Collateral damage is acknowledged with ceftriaxone, but the Adult Hospital Level Committee was of the opinion that all antibiotics result in collateral damage, but should be used responsibly.
Recommendation: Treatment protocol in severe cases of bronchiectasis retained as ceftriaxone IV, de-escalated to oral amoxicillin/clavulanic.
Rationale: There are no head-to-head RCTs comparing amoxicillin/clavulanic acid IV to ceftriaxone IV that could be retrieved from the published literature. Also, more rational to recommend ceftriaxone, IV due to cost (Daily costs for amoxicillin/clavulanic acid IV vs ceftriaxone, IV are R60.18 vs R5.88, respectively).
Level of Evidence: III Expert opinion

If pseudomonas infection is suspected or confirmed on culture:
Ciprofloxacin, oral: *retained and dose amended*
piperacillin /tazobactam, IV: *not added*
Cefepime, IV: *not added*
Azithromycin, oral: *not added for add-on therapy to beta-lactams*

External stakeholder comment received to consider additional options, cefepime, IV, piperacillin/tazobactam, IV and azithromycin, oral.

Ciprofloxacin, oral: The Adult Hospital Level Committee was of the opinion that oral ciprofloxacin was sufficient. Though for *Pseudomanas* in bronchiectasis, 30% resistance to ciprofloxacin has been reported, and therefore high dose ciprofloxacin has been recommended in this setting (noting that the pharmacodynamic profile of ciprofloxacin is concentration-dose dependant).

Macrolides: It is common knowledge not to use macrolides for eradication of *Pseudomonas aeruginosa*. Macrolides are essentially used with standard antibiotic treatment in patients with cystic fibrosis due to immunomodularly effect.
Recommendation: Ciprofloxacin, oral retained for pseudomonas infection and dose amended from '*500 mg 12 hourly'* to '*750 mg 12 hourly'.*
Level of Evidence: III Susceptibility data[34]

[33] Pasteur MC, Bilton D, Hill AT; British Thoracic Society Bronchiectasis non-CF Guideline Group. British Thoracic Society guideline for non-CF bronchiectasis.Thorax. 2010 Jul;65Suppl 1:i1-58.http://www.ncbi.nlm.nih.gov/pubmed/20627931
[34] NICD susceptibility data

16.4 CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

Description

Updated GOLD Guidelines, 2017[35] recommends FEV spirometry measurements to diagnose COPD. However, the Modified British Medical Research Council (mMRC) dyspnoea scale is used to monitor COPD[36], rather than FEV as the latter progressively worsens through the natural course of the disease. GOLD Guidelines state that "There is only a weak correlation between FEV1, symptoms and impairment of a patient's health status[37] [38]. For this reason, formal symptomatic assessment is also required". The mMRC is a simple measure of breathlessness that relates to other measures of health status and predicts future mortality risk.[39] [40]

Text in the STG updated to:

COPD is characterised by persistent respiratory symptoms (dyspnoea, chronic cough and sputum production), and airflow limitation. Spirometry is required to diagnose COPD, where the post bronchodilator FEV1/FVC ratio is < 0.7. COPD is likely to worsen over time, even with optimal care.

Regular follow-up is necessary to monitor lung function, symptoms, exacerbations, co-morbidities, and the need for treatment regimen changes.

COPD can be graded on severity of symptoms and frequency of exacerbations to assist in treatment selection and to monitor treatment success:

GOLD grade	mMRC breathlessness score	Exacerbations in past year
A	0–1	<2
B	≥2	<2
C	0–1	≥2
D	≥2	≥2

The mMRC scale:

Grade	Exacerbations in past year
0	Dyspnea with strenuous exercise
1	Dyspnea when hurrying on level ground or walking up a slight hill
2	Walks slower than people of same age group, due to dyspnea
3	Stops for breath after walking 91m, or after a few minutes on level ground
4	Too breathless to leave the house, or dyspnea when dressing/undressing

Url link to the modified Medical Research Council (mMRC) dyspnea scale calculator:
https://www.mdcalc.com/mmrc-modified-medical-research-council-dyspnea-scale

Antibiotic therapy:

Mild exacerbation

Amoxicillin, oral: *added*

Doxycycline, oral: *added for penicillin allergic patients*

Aligned with PHC STGs and EML, 2018.

[35] Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, Chen R, Decramer M, Fabbri LM, Frith P, Halpin DM, López Varela MV, Nishimura M, Roche N, Rodriguez-Roisin R, Sin DD, Singh D, Stockley R, Vestbo J, Wedzicha JA, Agustí A. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. Am J Respir Crit Care Med. 2017 Mar 1;195(5):557-582. https://www.ncbi.nlm.nih.gov/pubmed/28128970

[36] Fletcher CM. Standardised questionnaire on respiratory symptoms: a statement prepared and approved by the MRC Committee on the Aetiology of Chronic Bronchitis (MRC breathlessness score). BMJ 1960; 2: 1662.

[37] Jones PW. Health status and the spiral of decline. *COPD* 2009; **6**(1): 59-63.

[38] Han MK, Muellerova H, Curran-Everett D, et al. GOLD 2011 disease severity classification in COPD Gene: a prospective cohort study. *The Lancet Respiratory medicine* 2013; **1**(1): 43-50.

[39] Sundh J, Janson C, Lisspers K, Stallberg B, Montgomery S. The Dyspnoea, Obstruction, Smoking, Exacerbation (DOSE) index is predictive of mortality in COPD. Prim Care Respir J 2012; 21(3): 295-301.

[40] Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. Chest 2002; 121(5): 1434-40.

Moderate to severe exacerbation

Amoxicillin/clavulanic acid, oral: *retained*

The 2015 GERMS data[41] indicated that Invasive *Haemophilus* serotype b 27% resistant to amoxicillin and the non typeable was 11% resistant to amoxicillin, and therefore amoxicillin/clavulanic acid, oral recommended for all patients with a ***moderate to severe*** exacerbation

Level of Evidence: III Susceptibility data

Severe penicillin allergy

Azithromycin, oral: *deleted*

Moxifloxacin, oral: *added*

High levels of resistance to macrolides amongst pneumococcus.

Level of Evidence: III Susceptibility data[42]

CHRONIC THERAPY

Steps in treatment algorithm amended to reflect the GOLD Grade categories.

i. GRADE B

SABA, inhaler: *directions for use amended (LABA added to and not as replacement of SABA)*

LABA, inhaler: *directions for use amended (LABA added to and not as replacement of SABA); prescriber level amended*

GOLD Guidelines, 2017[43], states that *"regular as needed SABAs improves FEV1 and symptoms"* [44] and the algorithm in the STG was amended to recommend LABA added to and not as replacement of SABA.

Level of Evidence: III Guidelines

ii. GRADE C and D (Moderate to very severe COPD)

SABA PLUS LABA or LABA/ICS

SABA, inhaler: *added as standard maintenance therapy (see Grade B)*

LABA, inhaler: *added as standard maintenance therapy (see Grade B); prescriber level amended*

LABA/ICS, inhaler: *retained for exacerbations; prescriber level amended*

Long-acting muscarinic antagonists e.g.: tiotropium inhaler: *not added*

LABA/ICS: Moderate to very severe COPD and exacerbations responds more effectively to LABA/ICS than either component alone in improving lung function, health status and reducing exacerbations.[45] [46] However, RCT evidence suggests that ICS associated with higher prevalence of oral candidiasis, hoarse voice, skin bruising and pneumonia.[47]

Tiotropium reviewed by the Tertiary & Quaternary Committee, but not approved for inclusion to EML due to high cost[48].

Level of Evidence: III Guidelines

[41] GERMS 2015 susceptibility data, www.nicd.ac.za

[42] NICD susceptibility data

[43] GOLD 2017 Guidelines

[44] Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, Celli BR, Chen R, Decramer M, Fabbri LM, Frith P, Halpin DM, López Varela MV, Nishimura M, Roche N, Rodriguez-Roisin R, Sin DD, Singh D, Stockley R, Vestbo J, Wedzicha JA, Agustí A. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD Executive Summary. Am J Respir Crit Care Med. 2017 Mar 1;195(5):557-582. https://www.ncbi.nlm.nih.gov/pubmed/28128970

[45] Nannini LJ, Lasserson TJ, Poole P. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus long-acting beta(2)-agonists for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2012; **9**(9): CD006829.

[46] Nannini LJ, Poole P, Milan SJ, Kesterton A. Combined corticosteroid and long-acting beta(2)-agonist in one inhaler versus inhaled corticosteroids alone for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2013; **8**(8): CD006826.

[47] Yang IA, Clarke MS, Sim EH, Fong KM. Inhaled corticosteroids for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2012; 7(7): CD002991.

[48] T& Q EML, December 2019

16.6 PNEUMONIA, COMMUNITY ACQUIRED (CAP)

Diagnosis

Initial diagnostic chest x-ray: *management of patients with negative CXR*

Management of patients, who have a negative chest x-ray result, has been added, aligned with the South African Guidelines[49] for management of community-acquired pneumonia in adults, 2017. Following narrative has been added to the STG:

> CXR almost invariably shows a focal area of opacification or consolidation. However, empiric antibiotic therapy can be considered for severely ill hospitalised patients with suspected pneumonia and a negative CXR – pneumonia is excluded if repeat CXR after 24-48 hours still shows no opacification.
> ……..

Level of Evidence: III Guidelines

Follow-up chest x-ray: *criteria added*

Text of the STG was amended from:

"A follow-up CXR 4–6 weeks after completion of therapy should be done in all but very mild cases or in otherwise healthy adults, to ensure complete resolution of the pneumonia",

To:

"A follow-up CXR 4–6 weeks after completion of therapy should be done in patients >50 years of age, or if symptoms persist".

The initial recommendation in the Adult Hospital Level STGs and EML, 2015 edition (to ***not*** routinely repeat chest x-rays for patients with satisfactory clinical recovery from CAP), is aligned with guidelines.[50] [51]

Additional guidance added to clarify criteria for reimaging based on limited data that has been cited in these guidelines: *Follow-up chest x-ray recommended in patients with persistent symptoms and who are at risk of malignancy (the elderly; especially smokers or ex-smokers).*

Studies of CAP in hospital often exclude patients with lung cancer; but malignancy rates, in patients recovering from CAP has been reported as 1.3% to 4%.[52] [53] [54] [55] Observational cohort study by Tang et al[7] showed that risk factors associated with lung cancer (diagnosed after CAP) included age ≥50 years (aHR 19.0; 95% CI, 5.7 to 63.6), male sex (aHR, 1.8; 95% CI, 1.1to 2.9), and smoking (aHR, 1.7; 95% CI, 1.0 to 3.0). Longer-term study[56] reported that 9.2% of CAP survivors were newly diagnosed with cancer (predominantly elderly, smokers or ex-smokers and male) with a mean time to diagnosis of 297 days; though only 27% were diagnosed within 90 days of hospital discharge.

Level of Evidence: III Observational studies, Guidelines

[49] Boyles TH, Brink A, Calligaro GL, Cohen C, Dheda K, Maartens G, et al; South African Thoracic Society; Federation of Infectious Diseases Societies of Southern Africa. South African guideline for the management of community-acquired pneumonia in adults. J Thorac Dis. 2017 Jun;9(6):1469-1502. https://www.ncbi.nlm.nih.gov/pubmed/28740661

[50] Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019 Oct 1;200(7):e45-e67. https://www.ncbi.nlm.nih.gov/pubmed/31573350

[51] Lim WS, Baudouin SV, George RC, Hill AT, Jamieson C, Le Jeune I, Macfarlane JT, Read RC, Roberts HJ, Levy ML, Wani M, Woodhead MA; Pneumonia Guidelines Committee of the BTS Standards of Care Committee. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax. 2009 Oct;64 Suppl 3:iii1-55. https://www.ncbi.nlm.nih.gov/pubmed/19783532

[52] Macdonald C, Jayathissa S, Leadbetter M. Is post-pneumonia chest X-ray for lung malignancy useful? Results of an audit of current practice. Intern Med J 2015;45:329–334. https://www.ncbi.nlm.nih.gov/pubmed/25583286

[53] Holmberg H, Kragsbjerg P. Association of pneumonia and lung cancer: the value of convalescent chest radiography and follow-up. Scand J Infect Dis 1993;25:93–100. https://www.ncbi.nlm.nih.gov/pubmed/8460356

[54] Little BP, Gilman MD, Humphrey KL, Alkasab TK, Gibbons FK, Shepard JA, et al. Outcome of recommendations for radiographic follow-up of pneumonia on outpatient chest radiography. AJR Am J Roentgenol 2014;202:54–59. https://www.ncbi.nlm.nih.gov/pubmed/24370128

[55] Tang KL, Eurich DT,Minhas-Sandhu JK,Marrie TJ,Majumdar SR. Incidence, correlates, and chest radiographic yield of new lung cancer diagnosis in 3398 patients with pneumonia. Arch Intern Med 2011;171:1193–1198. https://www.ncbi.nlm.nih.gov/pubmed/21518934

[56] Mortensen EM, Copeland LA, Pugh MJ, Fine MJ, Nakashima B, Restrepo MI, de Molina RM, Anzueto A. Diagnosis of pulmonary malignancy after hospitalization for pneumonia. Am J Med. 2010 Jan;123(1):66-71. https://www.ncbi.nlm.nih.gov/pubmed/20102994

Empiric antimicrobial therapy

Duration of empiric antibiotic therapy: *amended*

Aligned with guidelines that advises that the *"precise duration of antibiotic therapy for the management of microbiologically documented and non-documented CAP is not informed by robust evidence. The duration of therapy should be determined based on the clinical response of the patient and the causative agent. When fever defervesces rapidly and there is clinical improvement it is safe to stop beta-lactam antibiotics after 5–7 days. In patients who show a slow clinical improvement or who have a confirmed aetiological agent such as Pseudomonas aeruginosa, S. aureus or gram-negative enteric organisms, it may be necessary to continue antibiotics for longer"*[57]*;*

And, "*that the duration of antibiotic therapy should be guided by a validated measure of clinical stability (resolution of vital sign abnormalities [heart rate, respiratory rate, blood pressure, oxygen saturation, and temperature], ability to eat, and normal mentation), and antibiotic therapy should be continued until the patient achieves stability and for no less than a total of 5 days……the duration of therapy for CAP due to suspected or proven MRSA or P. aeruginosa should be 7 days, in agreement with the recent hospital- acquired pneumonia and ventilator- associated pneumonia guidelines* ".[58]

Meta-analysis by Tansarli et al (2016) of 21 RCTs[59], suggests that short course antibiotic treatment (≤6 days) is as effective, but better in reducing mortality and side-effects than longer course treatment (≥7 days) in CAP:

- Clinical cure: RR= 0.99 (95% CI 0.97 to 1.01)
- Serious adverse events: RR= 0.73 (95% CI 0.55 to 0.97)
- Mortality: RR= 0.52 (95% CI 0.33 to 0.82).

Recommendation: Duration of empiric antibiotic in community acquired pneumonia be recommended as 5-7 days, guided by clinical response, with a minimum of 7 days for MRSA or *Pseudomonas.* However, longer duration of treatment recommended in following cases: pathogen identified that was not susceptible to initial empiric therapy; extrapulmonary infection (e.g. meningitis or endocarditis); empyema, lung abscess or necrotizing pneumonia or unusual organism present.

Rationale: Evidence of comparable effectiveness between shorter course (≤6 days) vs longer course (≥7 days) antibiotic therapy with better mortality and serious adverse event outcomes in community acquired pneumonia in adults. And, aligned with guidelines.

Level of Evidence: I Meta-analysis, Guidelines

The severity of pneumonia is no longer measured using the CURB score as it is a diagnostic rather than a prognostic score, but current definitions for severity of CAP includes the CURB score.

Community-acquired pneumonia without features of severe pneumonia

Severe penicillin allergy:

Moxifloxacin, IV: *added*

Moxifloxacin, oral: *retained*

STG amended as follows:

[57] Boyles TH, Brink A, Calligaro GL, Cohen C, Dheda K, Maartens G, et al; South African Thoracic Society; Federation of Infectious Diseases Societies of Southern Africa. South African guideline for the management of community-acquired pneumonia in adults. J Thorac Dis. 2017 Jun;9(6):1469-1502. https://www.ncbi.nlm.nih.gov/pubmed/28740661

[58] Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019 Oct 1;200(7):e45-e67. https://www.ncbi.nlm.nih.gov/pubmed/31573350

[59] Tansarli GS, Mylonakis E. Systematic Review and Meta-analysis of the Efficacy of Short-Course Antibiotic Treatments for Community-Acquired Pneumonia in Adults. Antimicrob Agents Chemother. 2018 Aug 27;62(9). pii: e00635-18. https://www.ncbi.nlm.nih.gov/pubmed/29987137

- 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 days.

Level of Evidence: III Expert opinion

Patients > 65 years or co-morbid disease (including HIV infection)

Ceftriaxone, IV: *retained*

Amoxicillin/clavulanic acid, IV: *not added*

Amoxicillin/clavulanic acid IV is cost-prohibitive with ceftriaxone currently the more affordable option. Also, aligned with recommendations by Engel et al, 2014)[60]

Level of Evidence: III Expert opinion

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

Ceftriaxone, IV: *retained*

Amoxicillin/clavulanic acid, IV: *not added*

Azithromycin, IV: *direction for use amended*

Amoxicillin/clavulanic acid IV is cost-prohibitive with ceftriaxone currently the more affordable option.

Duration of administration of azithromycin, IV amended to be aligned with SAMF 2016 as follows:

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

Level of Evidence: III Guidelines[61]

16.11.1 ISONIAZID MONORESISTANT TB

Levofloxacin, oral: *added*

Rifampicin, oral: *retained*

Ethambutol, oral: *retained*

Pyrazinamide, oral: *retained*

Isoniazid, oral (high-dose): *not added*

Refer to the medicine review, levofloxacin for INH-resistant TB (September 2019):

Levofloxacin for INH-resistant TB-Adı

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on this evidence review, the Adult Hospital Committee reccomends a levofloxacin-based regimen for treatment of INH-monoresistant TB, for a duration of 6 months. To assist with adherence, a fixed dose combination (FDC) product is preferred. Rifampicin, pyrazinamide and ethambutol are only available in a fixed dose combination product co-formulated with isoniazid. It is noted that this FDC is routinely prescribed in clinical practice for ease of administration by the patient, and levofloxacin can be added to this.

Rationale: Aligned with WHO conditional reccomendation with very low quality evidence[3].

Level of Evidence: III Individual patient data meta-analysis (observational data)[62]

[60] Engel MF, Bruns AH, Hulscher ME, Gaillard CA, Sankatsing SU, Teding van Berkhout F, Emmelot-Vonk MH, Kuck EM, Steeghs MH, den Breeijen JH, Stellato RK,Hoepelman AI, Oosterheert JJ. A tailored implementation strategy to reduce the duration of intravenous antibiotic treatment in community-acquired pneumonia: a controlled before-and-after study. Eur J Clin Microbiol Infect Dis. 2014 Nov;33(11):1897-908. doi: 10.1007/s10096-014-2158-z.https://www.ncbi.nlm.nih.gov/pubmed/24859925

[61] SAMF, 2016.

[62] Fregonese F, Ahuja SD, Akkerman OW, Arakaki-Sanchez D, Ayakaka I, Baghaei P, et al. Comparison of different treatments for isoniazid-resistant tuberculosis: an individual patient data meta-analysis. Lancet Respir Med. 2018;6(4):265-75. https://www.ncbi.nlm.nih.gov/pubmed/29595509

The Adult Hospital Committee notes that the upcoming updated draft NDoH DR-TB Guidelines also recommends adding high dose INH regardless of INH resistance subtype (*inhA* and/or *katG* mutations). Although the addition of high-dose INH can be expected to increase the effectiveness of the regimen when the INH resistance is caused by the *inhA* mutation alone, the high-level resistance typically caused by the *katG* mutation likely renders the addition of isoniazid futile. There is no evidence that adding high-dose INH in the presence of the *katG* mutation is beneficial. In addition, it contradicts WHO guidance, which states that "[in the presence of a *katG* mutation], the inclusion of isoniazid in the regimen, even at a higher dose, is unlikely to increase its effectiveness."[7] Furthermore, in South Africa, INH-resistance is initially determined genotypically, so the subtype of INH resistance (*inhA* vs *katG*) is almost always available to the clinician, allowing him/her to easily determine the appropriateness of adding high dose INH. *katG* mutations are also more common than *inhA* mutations in any case at the population level, as reported in the Free State[63]. Lastly, the addition of extra INH to the FDC adds to the pill burden and increases the risk of adverse events due to isoniazid.

NEMLC MEETING OF 5 DECEMBER 2019:

NEMLC accepted the proposal as recommended by the Adult Hospital Level Committee, above. The Global TB Programme report of 78.6% of 1174 isolates of rifampicin susceptible, isoniazid resistant TB presenting with mutations in the katG gene, was noted (article pending publication).

16.11.2 MULTIDRUG-RESISTANT TB

Injectable DR-TB regimen:

Kanamycin, injection: *deleted*
Moxifloxacin, oral: *deleted*
Ethionamide, oral: *deleted*
Terizidone, oral: *deleted*
Pyrazinamide, oral: *deleted*

The NEMLC had forwarded a position statement to the NDoH DR-TB Programme on the DR-TB Directorate's rolling out of interim DR TB guidelines which include unpublished regimens and unregistered medications, without following the National Essential Medicine List process - resulting in the programme being dependent on non-EML medicines (see below):

AdultHospitalLevel_
MDR-TB_NEMLC Pos

(Available on request)

A response was subsequently received from the NDoH Programme Director and members of the National Clinical Advisory Committee. However, NEMLC recommended that going forward, evidence reviews be developed, based on a critical appraisal of the evidence, for medicines recommended in the NDoH DR-TB interim guidelines (noting that the absolute effect sizes and NNT/NNH would still be required). The evidence reviews follow below:

Non-injectable DR-TB regimen:

Clofazimine, oral: *added with a condition*
Linezolid, oral: *added with a condition*
Bedaquiline, oral: *added with a condition*
Delaminid, oral: *added with a condition*

[63] Pitso L, Potgieter S, Van der Spoel van Dijk A. Prevalence of isoniazid resistance-conferring mutations associated with multidrug-resistant tuberculosis in Free State Province, South Africa. S Afr Med J. 2019 Aug 28;109(9):659-664. https://www.ncbi.nlm.nih.gov/pubmed/31635590

Levofloxacin, oral: *added with a condition*
Ethambutol, oral: *added with a condition*
Pyrazinamide, oral: *added with a condition*
Isoniazid, oral (high-dose): *added with a condition*

Evidence reviews have been developed for the individual DR-TB medicines as well as part of a regimen; noting that presently these medicines are recommended for long course therapy (The WHO MDR-TB Guidelines, 2019 recommendation for the standardised shorter course regimen is conditional with a low certainty of the effects).

OVERVIEW:

The overview document (September 2019) provides a narrative of the MDR Tuberculosis pharmacological management, and should be reviewed together with the individual medicine reviews for bedaquiline, linezolid, delaminid and clofazimine.

DR-TB Regimens - Overview-AdultRevie

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Provides an assessment of the evidence of the WHO MDR-TB Guidelines, 2019 versus the National Department of Health Interim MDR-TB Guidelines, 2018

i. Clofazamine for DR-TB (September 2019)

Clofazamine for DR-TB-Adult Review

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on the evidence review, the Adult Hospital Level Committee recommends that clofazimine not be included in the Adult Hospital Level EML that enables routine access of this medicine at all secondary level facilities. The medicine is recommended for use at designated MDR-TB facilities where appropriate susceptibility testing, monitoring and management of adverse events is possible; with relevant support from relevant Infectious Disease experts or Advisory Committees. It is acknowledged that the short-course DR-TB regimen is a conditional WHO recommendation and is currently administered nationally under operational research conditions**.** Clofazimine requires SAPHRA registration.

Rationale: There is evidence for clofazamine's efficacy as part of a multi-drug combination regimen for MDR TB. The severe adverse event rate is better than most of the current MDR-TB drugs. The need for individualised management of DR-TB requires particluar consideration.

Level of Evidence: I RCT[64]

Review indicator(s): **SAHPRA registration status, price**

ii. Linezolid for DR-TB (August 2019)

Linezolid for DR-TB_Adult Review

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on the evidence review, above, the Adult Hospital Level Committee recommends that linezolid not be included in the Adult Hospital Level EML (that enables routine access at all secondary level facilities). The medicine is recommended for use at designated MDR-TB

[64] Duan H, Chen X, Li Z, Pang Y, Jing W, Liu P, et al. Clofazimine improves clinical outcomes in multidrug-resistant tuberculosis: a randomized controlled trial. Clin Microbiol Infect. 2019;25(2):190-5. https://www.ncbi.nlm.nih.gov/pubmed/30036672

facilities where appropiate susceptibility testing, monitoring and management of adverse events is possible; with relevant support from relevant Infectious Disease experts or Advisory Committees. It is acknowledged that the short-course DR-TB regimen is a conditional WHO recommendation and is currently administered nationally under operational research conditions.

Rationale: Low quality of evidence for use of linezolid in MDR TB; noting the lack of efficacy and serious adverse events (i.e. optic neuritis/neuropathy, peripheral neuropathy and mylesuppresion). It is acknowledged that the results of STREAM II will be available in due course, as this RCT is currently still enroling study participants, that will further inform decision-making. The need for individualised management of DR-TB requires particluar consideration.

Level of Evidence: III Systemic review and meta-analyses of observational studies, Observational studies[65]

iii. Bedaquiline for DR-TB (June 2019)

Bedaquiline for DR-TB-Adult Review

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on the evidence review, the Adult Hospital Level Committee recommends that bedaquiline (BDQ) not be included in the Adult Hospital Level EML (that enables routine access at all secondary level facilities). The medicine is recommended for use at designated MDR-TB facilities where appropiate susceptibility testing, monitoring and management of adverse events is possible; with relevant support from relevant Infectious Disease experts or Advisory Committees. . It is acknowledged that the short-course DR-TB regimen is a conditional WHO recommendation and is currently administered nationally under operational research conditions.

Rationale: The evidence base for BDQ in MDR and XDR tuberculosis treatment regimens is limited; and is currently insufficient in terms of mortality outcomes. Additional RCT data on mortality would further inform decision-making. Phase 3 RCTs, including the STREAM2 trial are currently underway, that will permit firmer recommendations to be made in this regard. There is also currently insufficient high-quality evidence to recommend BDQ in pregnant women, HIV patients with CD4 <300, and severe extra-pulmonary or neurological disease. Outcomes with BDQ may be worse in important subgroups such as those with cavitatory disease, and BDQ requires periodic ECG monitoring due to its propensity to increase the QTc interval. The need for individualised management of DR-TB requires particluar consideration.

Level of Evidence: III Disease oriented RCTs[66] [67], Observational studies[68] [69] [70]

65 Singh B, Cocker D, Ryan H, Sloan DJ. Linezolid for drug-resistant pulmonary tuberculosis. Cochrane Database Syst Rev. 2019;3:CD012836. https://www.ncbi.nlm.nih.gov/pubmed/30893466

[66] Nunn AJ, Phillips PPJ, Meredith SK, Chiang CY, Conradie F, Dalai D, et al. A Trial of a Shorter Regimen for Rifampin-Resistant Tuberculosis. N Engl J Med. 2019;380(13):1201-13. https://www.ncbi.nlm.nih.gov/pubmed/30865791

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iv. Delaminid for DR-TB (June 2019)

Delamanid for DR-TB-Adult Review

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on this evidence review, the Adult Hospital Level Committee recommends that delaminid not be included in the Adult Hospital Level EML (that enables routine access at all secondary level facilities). The medicine is recommended for use at designated MDR-TB facilities where appropiate susceptibility testing, monitoring and management of adverse events is possible; with relevant support from relevant Infectious Disease experts or Advisory Committees.
It is acknowledged that the short-course DR-TB regimen is a conditional WHO recommendation and is currently administered nationally under operational research conditions.

Rationale: In the context of alternative regimens available to treat MDR-TB, delamanid is an expensive agent with no apparent reduction in mortality (either TB-attributable or overall). Furthermore, in the phase III RCT there was no treatment statistically significant difference in sputum culture conversion rates at 2 or 6 months. The need for individualised management of DR-TB requires particluar consideration.

Level of Evidence: III RCTs (phase I and II)[71] [72]; observational studies[73]

v. Isoniazid, oral (high-dose)

Refer to the discussion in section 16.11.1: INH monoresistant TB, above.

Summary:

- The Adult Hospital Level Committee does not recommend inclusion of the injectable-free DR-TB regimen to the Adult Hospital Level EML (that enables routine access at all secondary level facilities). Patients should be managed individually for MDR TB with drug susceptibility confirmed by laboratory (molecular or phenotypic, culture and sensitivity) results.
- There are designated MDR-TB facilities (available at all levels of care), where appropiate susceptibility testing, monitoring and management of adverse events is possible; with relevant support from relevant Infectious Disease experts or Advisory Committees.
- The evidence for oral short-course DR-TB regimen is uncertain and is a conditional WHO recommendation, currently administered nationally under operational research conditions[74].
- High dose isoniazid not be considered in the presence of *katG* mutations.
- Pending results from Phase III RCTs, including STREAM2 Trial[75], endTB clinical trial[76], endTB-Q clinical trial[77] should further inform decision-making on a possible standardised DR-TB regimen.

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[74] Letters by various international organisations (including MSF, TAC, DR-TB STAT, The Sentinel Project, The Union) to the WHO relating to the most recent DR-TB Guidelines, re-iterate that:*"…support for the use of shorter, all-oral treatment regimens under operational research conditions be made more explicit in the guidelines and supporting documents"; as "..it is unknown how the shorter regimen compares to the newly recommended, all-oral longer regimens",* amongst other concerns.
http://www.tbonline.info/media/uploads/documents/final_who_open_letter_drtb_tx_guidelines_4.23.19.pdf
https://www.theunion.org/news-centre/news/union-letter-to-who-regarding-treatment-guidelines

[75] The Evaluation of a Standard Treatment Regimen of Anti-tuberculosis Drugs for Patients With MDR-TB (STREAM). https://clinicaltrials.gov/ct2/show/NCT02409290

[76] Evaluating Newly Approved Drugs for Multidrug-resistant TB (endTB). https://clinicaltrials.gov/ct2/show/NCT02754765

[77] Evaluating Newly Approved Drugs in Combination Regimens for Multidrug-Resistant TB With Fluoroquinolone Resistance (endTB-Q) (endTB-Q). https://clinicaltrials.gov/ct2/show/NCT03896685

- However, South Africa has been reported to have an incidence of 30% pre-XDR, suggesting that the previous DR-TB programme was ineffective.

NEMLC MEETING OF 5 DECEMBER 2019:

NEMLC acknowledged the evidence reviews done by the Adult Hospital Level Committee; but recommended that DR-TB medicines be included on the national EML with a condition – "*all MDR-TB cases should be discussed with a designated specialist centre; and MDR-TB medicines to be accessed from these designated centre(s)".*

Rationale: Designated MDR-TB facilities are available at all levels of care - where appropiate susceptibility testing, monitoring and management of adverse events is possible; with relevant support from relevant Infectious Disease experts or Advisory Committees.

Kanamycin, IM: *not recommended for alternative indications*

Background: With the change of the NDoH DR-TB Guidelines, the regimen changed from kanamycin-containing regimen to short course injectable free regimen. Subsequently, Provinces have a surplus of kanamycin stock which is about to expire. The Adult Hospital Level Committee were requested to investigate the alternative use for this stock (estimated to be R1.5 million).

Review of the published literature did not produce any evidence for kanamycin for other indications other than DR-TB. Kanamycin injection is more painful than amikacin (included in the EML) and is ototoxic. If the aminoglycoside of choice in the previous DR-TB regimen was amikacin, this would have been easily resolved. Current available evidence shows that the non-injectable regimen is not non-inferior to the previous standard of care (injectable regimen). The Adult Hospital Level Committee also deliberated on the possibility of NDoH donating kanamycin stock to neighbouring Sub-Saharan countries that are still administering the injectable DR-TB regimens to patients - however, there may be ethical and regulatory concerns.

Summary: The Adult Hospital Level Committee was of the opinion that changes in Guidelines should prompt a phase-in/phase-out approach to transition to the updated policy recommendations to minimise wastage (e.g. as with the ART Programme) and this principle should be implemented across Programmes. Transparency in the guideline development process can assist with transitioning between guideline updates

PRETOMANID SCOPING REVIEW

Cochrane-SA was commissioned to do a scoping review of the evidence for pretomanid for MDR- and/or XDR-TB. Refer to the scoping document (October 2019):

Pretomanid_XDR-TB -Adults Scoping Rev

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: The Adult Hospital Level Committee acknowledges that there is currently insufficient evidence to inform a recommendation for pretomanid in MDR- or XDR-TB. However, a number of trials are underway (see Appendix 2 and 3), and the WHO is in the process of updating Guidelines for MDR-TB.

Review indicators: SAHPRA Registration, Evidence of efficacy and safety, Price reduction

Level of Evidence: III Phase 3 RCT

LATENT TUBERCULOSIS INFECTION (LTBI)

A: ISONIAZID

LTBI Regimens:

A. Isoniazid monotherapy

Isoniazid, oral: *duration of therapy retained as 12 months*

Refer to the medicine review: Isoniazid preventive therapy for PLHIV on ART (November 2018):

Isoniazid TB prophylaxis in PLHIV

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on this evidence review, the Adult Hospital Level Committee recommends a single six month course of INH within one month of initiating ART independent of CD4 cell count or TST status. Patients already on ART who have never received IPT may also benefit from IPT[5].

Rationale: Evidence of efficacy and safety with decreased TB incidence rate[5,6,8]. Badie *et al* showed that 6 months provided sustained response up to 6 years post treatment[7].

Level of evidence: I RCTs

NEMLC MEETING OF 21 FEBRUARY 2019:

Available evidence for IPT in PLHIV: Most of the evidence for isoniazid prevention therapy (IPT) in people living with HIV (PLHIV) was from the pre-ART era. Two RCTs done in PLHIV: i)RCT in Khayelitsha by Rangaka et al, 20146 of PLHIV either starting or established on ART comparing 12 months of isoniazid vs placebo; ii) Temprano RCT by Danel et al, 20157, where IPT; ART and IPT+ART were evaluated either starting early or late.

Previous NEMLC recommendation: In the PHC STGs and EML, 2018 IPT was simplified to 12 months, from the previous complex algorithm requiring TST, based on the Khayelitsha RCT.

Evidence for 6 months IPT: The Adult Hospital Level Committee's recommendation to change duration of IPT to 6 months based on a mortality benefit from the Temprano RCT, raised a concern. The Temprano RCT was done in West Africa, where the incidence of TB is lower compared to South Africa. It was stated that greater mortality benefit of 6 months IPT compared to 12 months IPT was biologically implausible, unless IPT is very toxic, however this is not the case.

Network meta-analysis of individual patient data (including South African data) is currently underway in the USA which should further inform decision-making on duration of IPT in PLHIV.

WHO recommendation of 36 months was discussed, noting that the evidence base was from the pre-ART era. IPT with ART was reported to be more durable than IPT without ART.

Recommendation: Previous NEMLC recommendation of IPT in PLHIV be retained as 12 months duration, until further evidence is forthcoming.

Rationale: Biologically plausible that 12 months rather than six months IPT would have greater benefit.

Despite the lack of data comparing duration of IPT therapy, available evidence in the local South African setting suggests that 12 months IPT would be reasonable.

Level of Evidence: I RCT

B: RIFAPENTINE

Following negotiations between UNITAIDs, Sanofi-Aventis South Africa (Pty) Ltd had reduced the price of rifapentine 150 mg, 24 tablets to R109.40 (55% reduction in price) – the current price on contract circular HP01-2019TB, w.e.f.7 November 2019.

Medicine review for rifapentine as part of the 3HP regimen for TB prophlaxis in PLHIV, has been updated using the updated tender price of rifapentine. Refer to the medicine review, rifapentine (3HP) as TPT in adult PLHIV (November 2019):

Rifapentine (3HP) as TPT in PLHIV -Adu

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Direct medicine price comparison shows that 3HP is still cost-prohibitive: 12H = R211.44 vs 3HP = R350.84 (Price parity will occur when rifapentine 150mg, 24 tablets is reduced further to ***R62.93***).

Recommendation: Based on this evidence review, The Adult Hospital Level Committee recommended that a rifapentine-isoniazid regimen probably has similar efficacy and safety to the current INH recommendation and could be considered as an alternative TLTBI option in PLHIV on an efavirenz or raltegravir based ART regimen. Given the non-inferiority in efficacy and slightly improved safety profile, cost would need to be comparable to the current recommendation of 12H.

Rationale: Current evidence does not show superior efficacy of short course HP to 6-12H.
HP showed decreased adverse events when compared to 6-9H, the adverse event rates reported for INH in these populations are not consistent with the adverse event rates reported from other South African studies. The improved completion rates are already factored into the efficacy results for HP owing to MITT analysis, the improved rates shown did not translate into superior efficacy of HP over 6-9H.
Level of Evidence: I RCTs (moderate quality).

New indications:

Additional indications proposed for 3HP to be tabled at a quorum NEMLC meeting for review, includes:
ii) Children < 5 years of age (though safety in <2 years of age is uncertain) – for review by Paediatric ERC
iii) Virologically suppressed on TEE & switching to TLD; or virologically suppressed on TLD – for review by Adult ERC

Refer to the medicine review for 3HP use in patients who are virally suppressed on TLD or TEE and switching to TLD (Medicine review: Rifapentine (3HP) as TPT in PLHOV on dolutegravir, November 2019):

Rifapentine (3HP) as TPT in PLHIV on D

http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults

Recommendation: Based on this evidence review, the Adult Hospital Level Committee concludes that in patients with suppressed viral load on DTG, 3HP could be considered as an alternative TLTBI option in PLHIV that are virally suppressed on a DTG-containing regimen. Given the non-inferiority in efficacy and slightly improved safety profile, cost would need to be comparable to the current recommendation of 12H.

Rationale: Preliminary data, suggests that rifapentine has no impact on patients who are already virally suppressed. Co-administration of DTG and HP was well tolerated with no HP-related adverse effects of ≥ grade 3. Although HP decreased DTG bioavailability, which was associated with a modest decrease in trough levels, all trough levels but one were above the DTG IC90. All viral loads were suppressed and DTG can be co-administered with HP without dose-adjustment.
Level of Evidence: III Phase I/II study

Review indicator: *Reduction in price; evidence of efficacy and safety*

NEMLC MEETINGS OF 11 APRIL 2019 AND 5 DECEMBER 2019:

The NEMLC recommended that 3HP prophylaxis could be considered as an alternative to 12H for Adult PLHIV on an efavirenz- or raltegravir-based ART regimen. However, 3HP was cost-prohibitive for inclusion to the Adult Hospital Level STGs and EML as a TPT regimen for PLHIV.

Rationale: There is reasonable evidence that the shorter 1HP and 3HP regimens are effective. However, there is no evidence of superior efficacy and safety over the current 12H standard of care; there are trends towards a slightly better side-effect profile for rifapentine-containing regimens, though it was uncertain whether the laboratory-confirmed (as opposed to clinically-evident) hepatoxic adverse effects would be relevant in the real-world setting. Furthermore, more data is required regarding drug-drug interactions (including in ART-naïve patients initiated on a DTG-containing regimen). Rifapentine is also considered too expensive and when there is price parity with 12H and adequate safety data (as provided by the TB Impact study and NDoH Demonstration study), the medicine could be further reviewed for possible inclusion in the EML.

Level of Evidence: I Meta-analysis[78], RCTs (moderate quality)[79] [80] [81]

Review indicators: *New evidence of efficacy and safety; Price*

Isoniazid +Rifapentine, oral: *not added*

Isoniazid, oral: *retained*

Non-inferiority trials suggests that 3HP prophylaxis is not inferior to 12H in PLHIV. However, 3HP is more expensive than 12H (even at a 55% reduction in the current price of rifapentine). Despite preliminary evidence suggesting that rifapentine can safely be used in patients on ART who are virally suppressed; peer reviewed publication of the Dolphin trial results is awaited.

Report prepared by TD Leong: Secretariat to the Adult Hospital Level Committee (2017-2020)

- *Information sourced from NEMLC ratified minutes and NEMLC-approved documents.*

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