COMMUNITY ACQUIRED PNEUMONIA

CHI Formulary Development Project

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Council of Health Insurance

INDICATION UPDATE

ADDENDUM- August 2023

To the CHI Original Community Acquired Pneumonia Clinical Guidance- Issued February 2020

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Related Documents

Related SOPs

- IDF-FR-P-02-01-IndicationsReview&IDFUpdates
- IDF-FR-P-05-01-UpdatedIndicationReview&IDFUpdates

Related WI:

- IDF-FR-WI-01-01SearchMethodologyGuideForNewIndications

Abbreviations

CADTH	Canadian Agency for Drugs and Technologies in Health
CAP	Community Acquired Pneumonia
CHI	Council of Health Insurance
CPG	Clinical Practice Guideline
CrCl	Creatinine Clearance
DRSP	Drug-Resistant *Streptococcus pneumoniae*
ERS	European Respiratory Society
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
ESICM	European Society of Intensive Care Medicine
ESKD	End Stage Kidney Disease
FQ	Fluoroquinolone
HAS	Haute Autorité de Santé
HTA	Health Technology Assessment
ICU	Intensive Care Unit
IDF	CHI Drug Formulary
IQWIG	Institute for Quality and Efficiency in Healthcare
MRSA	Methicillin-Resistant *Staphylococcus aureus*
MSSA	Methicillin-Sensitive *Staphylococcus aureus*
N/A	Not Available
NICE	National Institute for Health and Care Excellence
PBAC	Pharmaceutical Benefits Advisory Committee
sCAP	severe Community Acquired Pneumonia
SFDA	Saudi Food and Drug Authority
Spp	Species
VRE	Vancomycin-Resistant Enterococci

Executive Summary

Pneumonia is categorized as a lung infection that can result in respiratory difficulties and various symptoms. Community-acquired pneumonia (CAP) refers to the contraction of this infection within a community environment, excluding hospitals, nursing homes, and other healthcare facilities[1].

Globally, *Streptococcus pneumoniae* is the primary bacterium responsible for community-acquired pneumonia (CAP) in adults. Additionally, several other bacteria commonly associated with CAP include: *Hemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, Legionella spp., gram-negative bacilli, and *Staphylococcus aureus*[1].

The influenza virus, commonly known as the flu, is the predominant viral cause of CAP. Other viruses, such as parainfluenza virus, echovirus, adenovirus, and coxsackievirus, can also lead to CAP. In fact, viral infections are likely responsible for most cases of CAP. Additionally, fungi and parasites also have the potential to cause CAP[1].

The global occurrence of CAP is estimated to range from 1.5 to 14 cases per 1000 person-years[2].

Pneumonia significantly contributes to illness and death rates in Saudi Arabia. The occurrence and causes of this disease vary depending on the environment, with an approximate incidence of 1.5 to 2.5 cases per 1000 individuals annually for community-acquired pneumonia[3].

The primary objectives in treating patients with community-acquired pneumonia include eradicating the responsible pathogens, resolving clinical indications and symptoms, reducing the need for hospitalization, and preventing recurrent infections[4].

CHI issued community acquired pneumonia clinical guidance after thorough review of renowned international and national clinical guidelines in February 2020. Updating clinical practice guidelines (CPGs) is a crucial process for maintaining the validity of recommendations.

This report functions as an addendum to the prior CHI community acquired pneumonia clinical guidance and seeks to offer guidance for the effective management of CAP. It provides an **update on the community acquired pneumonia Guidelines** for CHI Formulary with the ultimate objective of updating the IDF (CHI Drug Formulary) while addressing **the most updated best available clinical and economic evidence related to drug therapies.**

Main triggers for the update are summarized, by being the addition of two new SFDA registered drugs **ceftobiprole** and **delafloxacin** and two non-SFDA registered

drugs effective for the treatment of community acquired pneumonia: **omadacycline** and **lefamulin**. Investigational drugs that are still under study and have not been approved by the FDA include solithromycin and nemonaxacin. Moreover, **new guidelines have been added to the report,** and include the Updates on community acquired pneumonia management in the ICU **2021**, the Severe community-acquired pneumonia: Current management and future therapeutic alternatives **2018**, the Recommendations and guidelines for the treatment of pneumonia in Taiwan **2019** and ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia **2023.**

After carefully examining clinical guidelines and reviewing the SFDA drug list, it is advisable to include the SFDA registered drug **ceftobiprole** (Zevtera®) and **delafloxacin** (Baxdela®) in the CHI formulary. It is also recommended to change certain prescribing edits related to previously listed drugs in the February 2020 CHI report: amoxicillin/clavulanic acid, ampicillin/sulbactam, piperacillin/tazobactam, cefuroxime, ceftriaxone, cefpodoxime, ceftaroline, cefotaxime, ceftazidime, cefepime, imipenem/cilastatin, meropenem, azithromycin, clarithromycin, erythromycin, doxycycline, gemifloxacin, moxifloxacin, vancomycin, clindamycin, linezolid and oseltamivir do not need “Prior Approval” (PA) as a prescribing edit. In addition, doxycycline was traditionally avoided in ages less than 8 years, but use has more recently been accepted for short courses (< 21 days) for all ages when necessary. Therefore, the prescribing edit “Age” should be changed from 12 years to 8 years and even permitted for all ages for short courses. To note that benzylpenicillin was withdrawn since the previous CHI report in February 2020.

Main recommendations issued by different Health Technology Assessment (HTA) bodies on the use of the current medications in Community acquired pneumonia were reviewed and summarized. These include the National Institute for Health and Care Excellence (NICE), the Canadian Agency for Drugs and Technologies in Health (CADTH), Haute Autorité de Santé (HAS), the Institute for Quality and Efficiency in Healthcare (IQWIG), and the Pharmaceutical Benefits Advisory Committee (PBAC). There was HTA analysis found for Ceftobiprole and Delafloxacin.

Table 1. Addition of New SFDA Registered Drugs for Community Acquired Pneumonia

MAJOR CHANGES		
Addition of New Molecules	**Drug Class**	**HTA Recommendations**
Ceftobiprole	Fifth generation cephalosporin	N/A
Delafloxacin	Fluoroquinolone	N/A

Table 2. Addition of Non-SFDA Registered Drug for Community Acquired Pneumonia

Addition of New Molecules	Drug Class
Omadacycline	Tetracycline
Lefamulin	Post semi-synthetic agent

Below is a table summarizing the major changes based on the different community acquired pneumonia guidelines used to issue this report:

Table 3. General Recommendations for the Management of Community Acquired Pneumonia

Management of Community-Acquired Pneumonia	
General Recommendations	**Level of Evidence/Grade of Recommendation and Reference**
With growing microbial resistance and continued need for appropriate coverage, several newer antibiotics have been studied in patients with CAP, with an ability to cover both typical, atypical and resistant CAP microbes, including newer generation cephalosporins, such as ceftaroline, ceftobiprole, ceftazidime-avibactam, and ceftolozane-tazobactam; newer macrolides like solithromycin; next generation fluoroquinolones like nemonoxacin zabofloxacin and delafloxacin; tetracyclines like omadacycline, and potent semisynthetic agents such as Lefamulin.	N/A[5]
Quinolones are preferred over macrolides if Legionella is suspected.	N/A[5]
To date the use of corticosteroids in patients with severe CAP remains controversial and it is not recommended by the most recent guidelines.	N/A[6]
Delafloxacin has shown a good in vitro and in vivo activity against major pathogens associated with sCAP including Streptococcus pneumoniae and methicillin-resistant Staphylococcus aureus (MRSA). It is also highly active against Legionella spp.	N/A[6]

At the end of the report, a **key recommendation synthesis section** is added highlighting the latest updates in **Community acquired pneumonia clinical and therapeutic management.**

Section 1.0 Summary of Reviewed Clinical Guidelines & Evidence

This section is divided into two parts: one part includes recommendations from **updated versions of guidelines** mentioned in the previous CHI Community Acquired Pneumonia report, and another part includes **newly added guidelines** that have helped generate this report.

1.1 Revised Guidelines

This section contains the **updated versions** of the guidelines detailed in the February 2020 CHI Community Acquired Pneumonia Report and the corresponding recommendations:

Table 4. Guidelines Requiring Revision

Guidelines requiring revision	
Old versions	**Updated versions**
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 2019	N/A*
Pneumonia (community-acquired): antimicrobial prescribing NICE guideline Published date: September 2019	N/A*
Management of community-acquired pneumonia in infants and children: Clinical practice guidelines endorsed by the Saudi Pediatric Infectious Diseases Society 2018	N/A*

**: No updated version available: the existing version is the most recent one and no further updates or revisions have been made or released.*

1.2 Additional Guidelines

This section includes the added guidelines to the previous CHI Community Acquired Pneumonia report, along with their recommendations.

Table 5. List of Additional Guidelines

Additional Guidelines
Updates on community acquired pneumonia management in the ICU 2021[5]
Severe community-acquired pneumonia: Current management and future therapeutic alternatives 2018[6]
Recommendations and guidelines for the treatment of pneumonia in Taiwan 2019[7]
ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia 2023[8]

1.2.1 Updates on Community Acquired Pneumonia Management in the ICU (2021)

This review published in 2021 focuses on the risk factors, microbiology, site of care decisions, and treatment of patients with severe CAP (sCAP). The major recommendations are highlighted below[5]:

- The current guidelines recommend the use of dual antibiotics: a β-lactam plus either a macrolide or a respiratory quinolone (levofloxacin or moxifloxacin) for patients with severe pneumonia in the ICU, with no risks for drug resistant organisms.
- Although the guideline provides direction on the best treatment strategies, several important controversies have emerged regarding the optimal course and choices of antibiotics in SCAP treatment. These include:
    - Combination therapy vs. monotherapy treatment strategy.
    - Optimal treatment with a β-lactam plus macrolide versus β-lactam plus fluoroquinolone.
    - Need for additional antibiotics directed towards drug resistant or PES pathogens.
    - Need for antibiotics in patients with identified viral pathogen.
    - Optimal duration of treatment.
    - Addition of corticosteroids.
- Quinolones are preferred over macrolides if Legionella is suspected.

- With growing microbial resistance and continued need for appropriate coverage, several newer antibiotics have been studied in patients with CAP, with an ability to cover both typical, atypical and resistant CAP microbes, including newer generation cephalosporins, such as ceftaroline, ceftobiprole, ceftazidime-avibactam, and ceftolozane-tazobactam; newer macrolides like solithromycin; next generation fluoroquinolones like nemonoxacin zabofloxacin and delafloxacin; tetracyclines like omadacycline, and potent semisynthetic agents such as Lefamulin.

Table 6. Newer Antibiotics for the Treatment of Community Acquired Pneumonia

Drug name	Class	Activity	Dose (Intravenous)
Ceftaroline	5th generation Cephalosporin	Gram-positive including resistant pneumococcus and MRSA and Gram-negatives	600 mg every 12 hours
Ceftobiprole	5th generation Cephalosporin	Extended spectrum activity against Gram-positive, MSSA, Methicillin resistant coagulase negative Staph, DRSP, and Gram-negatives including Pseudomonas and Enterobacteriaceae. No activity against MRSA.	500 mg every 8 hours
Solithromycin	4th generation macrolide	S. pneumoniae, H. influenzae, atypical pathogens and macrolide resistant organisms	400 mg every 24 hours
Nemonaxacin	Non-fluorinated quinolone	MRSA, DRSP and ertapenem-non-susceptible Enterobacteriaceae	750 mg every 24 hours
Delafloxacin	Novel fluoroquinolone	Gram-positives including drug resistant S. pneumoniae (penicillin-, macrolide-, multiple-drug resistant), fastidious Gram-negative pathogens including Hemophilus	300 mg every 12 hours

		species (β-lactamase producing, macrolide-non-susceptible) and S. aureus (MRSA, fluoroquinolone-non-susceptible MSSA)	
Omadacycline	Aminomethycycline	H. influenzae, M. catarrhalis, Legionella, Chlamydia, Mycoplasma, MRSA, DRSP, Streptococcus pyogenes, Streptococcus agalactiae and VRE. Not effective against Proteus, Providencia, Pseudomonas, and Morganella.	100 mg every 12 hours for two doses, then 100 mg every 24 hours
Lefalumin	Semi-synthetic Pleuromutilin	Gram-positive pathogens including DRSP and MRSA, fastidious Gram-negative pathogens and atypical pathogens including M. pneumoniae (including macrolide-resistant strains), C. pneumoniae, and L. pneumophila.	150 mg every 12 hours

1.2.2 Severe Community-Acquired Pneumonia: Current Management and Future Therapeutic Alternatives (2018)

The recommendations issued by this expert review of anti-infective therapy are prominent to be included in this report. They are highlighted below:

- Cefotaxime or ceftriaxone are by far the most recommended β-lactams in sCAP.
- Combined therapy has been linked to a lower mortality in sCAP.
- Legionella pneumophila and gram-negative bacilli have been identified as risk factors associated with early failure in hospitalized patients with CAP.

- Fluoroquinolones exhibit a high activity against L. pneumophila even superior to older macrolides (erythromycin, methymycin, pikromycin, oleandomycin, lankamycin, carbomycin, niddamycin and tylosin).
- Risk factors for sCAP caused by Gram-negative bacilli, including Pseudomonas aeruginosa, must be considered for selecting antimicrobials with high activity against these pathogens. In the empirical regimen, the substitution of a third-generation cephalosporin (cefotaxime or ceftriaxone) for an antipseudomonal β-lactam (piperacillin- tazobactam, cefepime, or meropenem) is judicious.
- Ceftaroline should be reserved for patients with microbiologically confirmed CAP due to penicillin-resistant S. pneumoniae (penicillin MIC ≥8 mg/L) or MRSA. Nevertheless, ceftaroline may be considered as a future option for empirical therapy in areas with high prevalence of MRSA or penicillin-resistant pneumococci and not be reserved exclusively for treatment failures.
- To date the use of corticosteroids in patients with severe CAP remains controversial and it is not recommended by the most recent guidelines.
- Delafloxacin has shown a good in vitro and in vivo activity against major pathogens associated with sCAP including Streptococcus pneumoniae and methicillin-resistant Staphylococcus aureus (MRSA). It is also highly active against Legionella spp.
- Zabofloxacin is another novel fluoroquinolone agent with potent activity against gram-positive pathogens including penicillin-resistant and levofloxacin resistant Streptococcus pneumoniae.
- Solithromycin is a novel macrolide with a potent in vitro activity against the most common pathogens, including macrolide-, penicillin-, and fluoroquinolone-resistant isolates of S. pneumoniae, as well as atypical bacterial pathogens. Solithromycin exhibits higher anti-inflammatory power than macrolides69, which may constitute an additional benefit for treatment of sCAP.

1.2.3 Recommendations and Guidelines for the Treatment of Pneumonia in Taiwan (2019)

Table 7. Quality of Evidence with the Equivalent Letter from the Taiwan Guideline

Quality of evidence	
High	A
Moderate	B
Low	C

Very low	D

Table 8. Strength of Recommendations with the Equivalent Number from the Taiwan Guideline

Strength of recommendations	
Strong	1
Weak	2

The recommendations issued by this guideline are highlighted below:

Empirical antimicrobial therapy

CRB-65 score, and CURB-65 score are used to evaluate the severity of CAP in this guideline.

1. No comorbidities, and no history of antibiotic treatment in the recent 3 months

For patients without comorbidities and recent history of exposure to antimicrobial agents, monotherapy with a b-lactam antibiotic or a non-b-lactam drug for atypical pathogens (mainly for Mycoplasma or Chlamydophila infection), such as macrolides or tetracyclines, is recommended. The selection of antimicrobial agent depends on the patient's clinical manifestations and contact history.

2. With comorbidities, or history of antibiotic treatment in the recent 3 months

For patients with comorbidities or recent history of exposure to antimicrobial agents, b-lactam monotherapy with or without addition of a macrolide are both optimal choices. Fluoroquinolones are listed as an alternative. Decision depends on the physician's clinical judgment, based on the individual patient's condition.

Inpatient, non-ICU admission, with low severity (CURB-65 0-1)

For patients admitted not primarily for the treatment of pneumonia, but for other medical concerns, e.g., multiple comorbidities, single elderly incapable of self-care, disabled patients who are unable to follow up at outpatient clinics, the recommended empirical antibiotics regimen is like those for the outpatient group. Intravenous antibiotics may be used for patients with gastrointestinal discomfort or malabsorption.

Inpatient, non-ICU admission, with moderate severity (CURB-65 2-3)

For CAP patients with moderate severity and CURB-65 score >= 2, we recommend combination therapy with a b-lactam antibiotic and a macrolide (1B). Fluoroquinolone (FQ) is listed as an alternative. Use of intravenous tigecycline is found to be associated with increased all-cause mortality compared to the control in

a meta-analysis of phase III and IV clinical trials. The U.S. Food and Drug Administration issued a boxed warning to the tigecycline drug label. Consultation of an infectious disease specialist is recommended when considering tigecycline use.

Inpatient, ICU admission, with high severity (CURB-65 4-5)

For patients with high disease severity requiring ICU admission, combination therapy with a b-lactam plus either a macrolide or a FQ is recommended. In this group of patients, there is no good evidence to confirm which of these two combinations is more efficacious (2D).

1.2.4 ERS/ESICM/ESCMID/ALAT Guidelines for the Management of Severe Community-Acquired Pneumonia (2023)

The European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Latin American Thoracic Association (ALAT) launched a task force to develop the first international guidelines for sCAP. The joint recommendations were published in 2023 and are summarized below[8].

Table 9. Levels of Recommendation

Level of Recommendation	Definition
Strong recommendation	The panel was certain that the desirable effects of the intervention outweighed the undesirable effects, and a strong recommendation against was made when the opposite was true.
Conditional recommendation	When desirable effects probably outweighed the undesirable effects, but appreciable uncertainty exists; a conditional recommendation against an intervention was made when the opposite was true.

Table 10. Recommendations from the ERS/ESICM/ESCMID/ALAT 2023 Clinical Guidelines

Recommendation	Strength of Recommendation/Level of Evidence
If the technology is available, the guideline suggests sending a lower respiratory tract sample (either	Conditional recommendation, very low

sputum or endotracheal aspirates) for multiplex PCR testing (virus and/or bacterial detection) whenever non-standard sCAP antibiotics are prescribed or considered	quality of evidence
In patients with sCAP and acute hypoxaemic respiratory failure not needing immediate intubation, we suggest using high-flow nasal oxygen (HFNO) instead of standard oxygen	Conditional recommendation, very low quality of evidence
The guideline recommends the addition of macrolides, not fluoroquinolones, to beta-lactams as empirical antibiotic therapy in hospitalized patients with sCAP	Conditional recommendation, very low quality of evidence
The duration of treatment of macrolides is set to be between 3 and 5 days. This would be reasonable timing especially in the context of de-escalation therapy.	Not graded
In patients with sCAP, we suggest the use of corticosteroids if shock is present	Conditional recommendation, low quality of evidence

2.0 Drug Therapy

This section comprises four subsections: the first one contains the newly recommended drugs SFDA registered, the second one covers drug modifications, the third one outlines the drugs that have been withdrawn from the market and the fourth one contains other drugs that are FDA approved but not SFDA registered.

2.1 Additions

After February 2020, there have been two new drugs that have received FDA and EMA approval and are SFDA registered. This section will include all characteristics describing Ceftobiprole and Delafloxacin as well as their HTA analysis respectively.

2.1.1 Ceftobiprole

The following table describes the characteristics of drug Ceftobiprole[9–11].

Table 11. Ceftobiprole Drug Information

SCIENTIFIC NAME **Ceftobiprole**	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	J18.9
Drug Class	Antibiotic
Drug Sub-class	Cephalosporin (fifth generation)
ATC Code	J01DI01
Pharmacological Class (ASHP)	Antibiotic, cephalosporin (fifth generation)
DRUG INFORMATION	
Dosage Form	Powder for concentrate for solution for infusion
Route of Administration	Intravenous use
Dose (Adult) [DDD]*	**Community-acquired pneumonia:** IV: 500 mg every 8 hours. Total duration (including oral step-down therapy) is a minimum of 5 days (or 7 days if methicillin-resistant S. aureus

	[MRSA] is isolated).
Maximum Daily Dose Adults*	1500mg
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	- CrCl 50 to 150 mL/minute: No dosage adjustment necessary. - CrCl 30 to <50 mL/minute: 500 mg every 12 hours. - CrCl <30 mL/minute: 250 mg every 12 hours. - ESKD without dialysis: 250 mg every 24 hours. - Augmented renal clearance (CrCl >150 mL/minute): IV: No dosage adjustment necessary; however, duration of infusion should be extended to 4 hours. - Hemodialysis, intermittent (thrice weekly): Dialyzable (~70%): IV: 250 mg every 24 hours.
Prescribing edits*	Age
AGE (Age Edit): not studied in pediatric population, therefore, restrict the use of ceftobiprole for age>18 years.	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): N/A	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Nausea, headache, drowsiness, diarrhea, vomiting, abdominal pain, dyspepsia, dysgeusia, fungal infections in different parts of your body, hyponatremia. **Most serious**: Hypersensitivity, phlebitis, infusion site reaction, increased serum

	creatinine and serum alanine aminotransferase.
Drug Interactions*	**Category X**: BCG (intravesical) Cholera vaccine Fecal Microbiota (Live) (Oral) Fecal Microbiota (Live) (Rectal)
Special Population	N/A
Pregnancy	Adverse events were not observed in animal reproduction studies.
Lactation	It is not known if ceftobiprole is present in breast milk. Due to the potential for serious adverse reactions in the infant, the manufacturer recommends a decision be made whether to discontinue breastfeeding or to discontinue the drug, considering the importance of treatment to the mother.
Contraindications	Hypersensitivity to ceftobiprole, other cephalosporins, or any component of the formulation; immediate and severe hypersensitivity (e.g., anaphylaxis) to any other type of beta-lactams
Monitoring Requirements	Renal function; signs/symptoms of hypersensitivity
Precautions	- Electrolyte abnormalities Sodium content should be considered in patients requiring sodium restriction. - Hemolytic anemia: If anemia develops during or after treatment, consider drug-induced hemolytic anemia. - Hypersensitivity: Use caution if initiating therapy in patients with a history of nonsevere hypersensitivity to other beta-lactam drugs.

	- Renal toxicity: Correct hypovolemia to maintain normal urinary output in patients receiving ceftobiprole. - Superinfection: Use may result in fungal or bacterial superinfection. Clostridioides difficile–associated diarrhea (CDAD) and pseudomembranous colitis have been reported with use. - Renal impairment: Use with caution in patients with renal impairment. Dosage adjustment is required with CrCl <50 mL/minute and prolongation of infusion is recommended in patients with CrCl >150 mL/minute. - Seizure disorders: Use with caution in patients with a history of seizure or CNS disorder.
Black Box Warning	[Canadian Boxed Warning]: Anaphylaxis, occasionally fatal, has been reported with use of beta-lactam antibiotics, including ceftobiprole; individuals with prior hypersensitivity reactions to multiple allergens may be at increased risk. Prior to initiating therapy with ceftobiprole, carefully assess patient for prior history of hypersensitivity to cephalosporins, penicillin, or other allergens.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The below table shows that there are no health technology assessment recommendations for Ceftobiprole for community acquired pneumonia.

Table 12. HTA Analysis for Ceftobiprole

Ceftobiprole	
CADTH	N/A
IQWIG	N/A
PBAC	N/A
NICE	N/A
HAS	N/A

CONCLUSION STATEMENT – CEFTOBIPROLE

Ceftobiprole, a fifth-generation cephalosporin, has an extended spectrum of activity against gram-positive bacteria, MSSA, Methicillin resistant coagulase negative Staph, DRSP, and Gram-negatives including Pseudomonas and Enterobacteriaceae but no activity against MRSA. It can be used in adults at a dose of 500mg every 8 hours if renal function is normal. Make sure to adjust dosage for renal impairment.

2.1.2 Delafloxacin

The following table describes the characteristics of drug Delafloxacin[12–14].

Table 13. Delafloxacin Drug Information

SCIENTIFIC NAME Delafloxacin	
SFDA Classification	Prescription
SFDA Approval	Yes
US FDA	Yes
EMA	Yes
MHRA	Yes
PMDA	Yes
Indication (ICD-10)	J18.9
Drug Class	Antibiotic
Drug Sub-class	Fluoroquinolone
ATC Code	J01MA
Pharmacological Class (ASHP)	Antibiotic, fluoroquinolone
DRUG INFORMATION	
Dosage Form	Powder for concentrate for solution for infusion and tablet
Route of Administration	Intravenous use and oral use
Dose (Adult) [DDD]*	**Community-acquired pneumonia:**

	Oral: 450 mg every 12 hours. IV: 300 mg every 12 hours. Duration of therapy: Duration is a minimum of 5 days.
Maximum Daily Dose Adults*	N/A
Dose (pediatrics)	N/A
Maximum Daily Dose Pediatrics*	N/A
Adjustment	Oral, IV: - Estimated glomerular filtration rate (eGFR) 30 to 89 mL/minute/1.73 m2: No dosage adjustment necessary. - eGFR 15 to 29 mL/minute/1.73 m2: Oral: No dosage adjustment necessary. IV: 200 mg every 12 hours - eGFR <15 mL/minute/1.73 m2: Use is not recommended. - ESRD on hemodialysis: Use is not recommended.
Prescribing edits*	Age, ST
AGE (Age Edit): This medicine must not be used in children and adolescents as it has not been studied enough in these groups, therefore, restrict the use of delafloxacin for age>18 years.	
CU (Concurrent Use Edit): N/A	
G (Gender Edit): N/A	
MD (Physician Specialty Edit): N/A	
PA (Prior Authorization): N/A	
QL (Quantity Limit): N/A	
ST (Step Therapy): Clinical experience is limited; some experts reserve for patients who cannot take other agents	
EU (Emergency Use Only): N/A	
PE (Protocol Edit): N/A	
SAFETY	
Main Adverse Drug Reactions (Most common and most serious)	**Most common:** Fungal infection, Headache, Vomiting, Increase in the number of transaminases, Itching, bradycardia. **Most serious**: -Hypersensitivity signs: Difficulty in

	swallowing or difficulty in breathing and cough; swelling of your lips, face, throat, or tongue; dry throat or throat tightening and severe rash. - Drop in blood pressure; blurred vision; dizziness.
Drug Interactions*	**Category X**: BCG (intravesical) Cholera vaccine Fecal Microbiota (Live) (Oral) Fecal Microbiota (Live) (Rectal) Nadifloxacin Strontium Ranelate
Special Population	- Older adult: Adverse effects (e.g., tendon rupture) may be increased in elderly patients. - G6PD deficiency: Hemolytic reactions may (rarely) occur with fluoroquinolone use in patients with G6PD deficiency.
Pregnancy	Adverse events were observed in some animal reproduction studies.
Lactation	It is not known if delafloxacin is present in breast milk. According to the manufacturer, the decision to breastfeed during therapy should consider the risk of infant exposure, the benefits of breastfeeding to the infant, and benefits of treatment to the mother.
Contraindications	Hypersensitivity to delafloxacin, other fluoroquinolones, or any component of the formulation.
Monitoring Requirements	WBC, signs of infection, serum creatinine; signs and symptoms of disordered glucose regulation
Precautions	- Aortic aneurysm and

	dissection: Fluoroquinolones should not be used in patients with a known history of aortic aneurysm or those at increased risk. - Glucose regulation: Diabetic patients should be monitored closely for signs/symptoms of disordered glucose regulation. Discontinue if a hypoglycemic reaction occurs and immediately initiate appropriate therapy. - Hypersensitivity reactions: Discontinue therapy at the first sign of skin rash or any other sign of a hypersensitivity reaction. - CNS effects: discontinue immediately and avoid further use of fluoroquinolones in patients who experience these reactions. Use with caution in patients with known or suspected CNS disorder, or risk factors that may predispose to seizures or lower the seizure threshold. - Peripheral neuropathy: Discontinue if symptoms of sensory or sensorimotor neuropathy occur. Avoid use in patients who have previously experienced peripheral neuropathy. - Psychiatric reactions: Use it with caution in patients with a history of or risk factor for depression. Reactions may occur following the first dose; discontinue if reaction occurs and institute appropriate therapy. - Tendinopathy/Tendon rupture: Discontinue at first sign of tendon pain, swelling, inflammation, or rupture. Avoid use in patients with a

	history of tendon disorders or who have experienced tendinopathy or tendon rupture. - Superinfection: Prolonged use may result in fungal or bacterial superinfection, including C. difficile-associated diarrhea (CDAD) and pseudomembranous colitis. - Renal impairment: Use with caution and reduce dose in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] 15 to 29 mL/minute/1.73 m2). Use is not recommended in patients with end-stage renal disease (eGFR <15 mL/minute/1.73 m2).
Black Box Warning	- Serious adverse reactions: Fluoroquinolones are associated with disabling and potentially irreversible serious adverse reactions that have occurred together, including tendinopathy and tendon rupture, peripheral neuropathy, and CNS effects. Discontinue delafloxacin immediately and avoid the use of fluoroquinolones in patients who experience any of these serious adverse reactions. - Exacerbation of myasthenia gravis: Fluoroquinolones may exacerbate muscle weakness in patients with myasthenia gravis. Avoid delafloxacin in patients with a known history of myasthenia gravis.
REMS*	N/A

HEALTH TECHNOLOGY ASSESSMENT (HTA)

The below table shows that there are no health technology assessment recommendations for Delafloxacin for community acquired pneumonia.

Table 14. HTA Analysis of Delafloxacin

Delafloxacin	
NICE	N/A
IQWIG	N/A
PBAC	N/A
CADTH	N/A
HAS	N/A

CONCLUSION STATEMENT – DELAFLOXACIN

Delafloxacin, a fluoroquinolone antibiotic, covers gram-positives including drug resistant S. pneumoniae (penicillin-, macrolide-, multiple-drug resistant), fastidious Gram-negative pathogens including Hemophilus species (β-lactamase producing, macrolide-non-susceptible) and S. aureus. It is only approved for adults. It can be used orally or intravenously as specified dose. Make sure to adjust according to creatinine clearance.

2.2 Modifications

Please refer to section 2.1.1.6 in the previous report to highlight these modifications:

- Amoxicillin/clavulanic acid does not need PA as a prescribing edit.
- Ampicillin/sulbactam does not need PA as a prescribing edit.
- Piperacillin/tazobactam does not need PA as a prescribing edit.

Please refer to section 2.1.2.6 in the previous report to highlight these modifications:

- Cefuroxime does not need PA as a prescribing edit.
- Ceftriaxone does not need PA as a prescribing edit.
- Cefpodoxime does not need PA as a prescribing edit.
- Ceftaroline does not need PA as a prescribing edit.
- Cefotaxime does not need PA as a prescribing edit.
- Ceftazidime does not need PA as a prescribing edit.
- Cefepime does not need PA as a prescribing edit.

Please refer to section 2.1.3.4 in the previous report to highlight these modifications:

- Imipenem/cilastatin does not need PA as a prescribing edit.
- Meropenem does not need PA as a prescribing edit.

Please refer to section 2.2.1.6 in the previous report to highlight these modifications:

- Azithromycin does not need PA as a prescribing edit.
- Clarithromycin does not need PA as a prescribing edit.

- Erythromycin does not need PA as a prescribing edit.

Please refer to section 2.3.1.4 in the previous report to highlight these modifications:

- Doxycycline does not need PA as a prescribing edit. AGE
- Doxycycline was traditionally avoided in ages < 8 years, but use has more recently been accepted for short courses (< 21 days) for all ages when necessary. Therefore, the prescribing edit Age should be changed from 12 years to 8 years and even permitted for short courses.

Please refer to section 2.4.1.7 in the previous report to highlight these modifications:

- Gemifloxacin does not need PA as a prescribing edit.
- Levofloxacin does not need PA as a prescribing edit.
- Moxifloxacin does not need PA as a prescribing edit.

Please refer to section 2.5.1.7 in the previous report to highlight these modifications:

- Vancomycin does not need PA as a prescribing edit.
- Clindamycin does not need PA as a prescribing edit.
- Linezolid does not need PA as a prescribing edit.

Please refer to section 2.6.1.6 in the previous report to highlight these modifications:

- Oseltamivir does not need PA as a prescribing edit.

2.3 Delisting

Benzylpenicillin was withdrawn from the previous CHI in February 2020.

2.4 Other Drugs

2.4.1 Omadacycline

FDA approves Nuzyra® (Omadacycline) in October 2018[15].

EMA approves Nuzyra® (Omadacycline) in October 2019[16].

According to the Updates on community acquired pneumonia management in the ICU 2021, with growing microbial resistance and continued need for appropriate coverage, several newer antibiotics have been studied in patients with CAP, with an ability to cover both typical, atypical, and resistant CAP microbes, including newer tetracyclines like Omadacycline[5].

The recommended dose of Omadacycline for pneumonia, community acquired (without risk factors for pseudomonas) is[17]:

- IV: 200 mg as a single dose or 100 mg twice daily on day 1, then 100 mg once daily.

- Oral: 300 mg twice daily on day 1, then 300 mg once.

Duration of therapy: Minimum of 5 days.

2.4.2 Lefamulin

FDA approves Xenleta® (Lefamulin) in August 2019[18].

EMA approves Xenleta® (Lefamulin) in July 2020[19].

According to the Updates on community acquired pneumonia management in the ICU 2021, with growing microbial resistance and continued need for appropriate coverage, several newer antibiotics have been studied in patients with CAP, with an ability to cover both typical, atypical, and resistant CAP microbes, including potent semisynthetic agents such as Lefamulin[5].

The recommended dose of Lefamulin for pneumonia, community acquired (alternative agent for patients unable to tolerate beta lactams or fluoroquinolones) is[20]:

- Oral: 600 mg every 12 hours.
- IV: 150 mg every 12 hours.

Duration of therapy: Total duration (which may include oral step-down therapy) is a minimum of 5 days.

Section 3.0 Key Recommendations Synthesis

- With growing microbial resistance and continued need for appropriate coverage, several newer antibiotics have been studied in patients with CAP, with an ability to cover both typical, atypical and resistant CAP microbes, including newer generation cephalosporins, such as ceftaroline, ceftobiprole, ceftazidime-avibactam, and ceftolozane-tazobactam; newer macrolides like solithromycin; next generation fluoroquinolones like nemonoxacin zabofloxacin and delafloxacin; tetracyclines like omadacycline, and potent semisynthetic agents such as Lefamulin[5].
- To date the use of corticosteroids in patients with severe CAP remains controversial and it is not recommended by the most recent guidelines[6].
- Delafloxacin has shown a good in vitro and in vivo activity against major pathogens associated with sCAP including Streptococcus pneumoniae and methicillin-resistant Staphylococcus aureus (MRSA). It is also highly active against Legionella spp[6].

Section 4.0 Conclusion

This report serves as **an annex to the previous CHI Community acquire pneumonia report** and aims to provide recommendations to aid in the management of Community acquired pneumonia. It is important to note that these recommendations should be utilized to support clinical decision-making and not replace it in the management of individual patients with CAP. Health professionals are expected to consider this guidance alongside the specific needs, preferences, and values of their patients when exercising their judgment.

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Section 6.0 Appendices

Appendix A. Prescribing Edits Definition

Prescribing edits Tools	Description
AGE (Age):	Coverage may depend on patient age
CU (Concurrent Use):	Coverage may depend upon concurrent use of another drug
G (Gender):	Coverage may depend on patient gender
MD (Physician Specialty):	Coverage may depend on prescribing physician's specialty or board certification
PA (Prior Authorization):	Requires specific physician request process
QL (Quantity Limits):	Coverage may be limited to specific quantities per prescription and/or time period
ST (Step Therapy):	Coverage may depend on previous use of another drug
EU (Emergency Use only):	This drug status on Formulary is only for emergency use
PE (Protocol Edit):	Use of drug is dependent on protocol combination, doses, and sequence of therapy

Appendix B. Community Acquired Pneumonia Scope

Section	Rationale/Updates
Updates on community acquired pneumonia management in the ICU 2021[5]	The current guidelines recommend the use of dual antibiotics: a β-lactam plus either a macrolide or a respiratory quinolone (levofloxacin or moxifloxacin) for patients with severe pneumonia in the ICU, with no risks for drug resistant organisms. Although the guideline provides direction on the best treatment strategies, several important controversies have emerged regarding the optimal course and choices of antibiotics in SCAP treatment. These include: (a) combination therapy vs. monotherapy treatment strategy, (b) optimal treatment with a β-lactam plus macrolide versus β-lactam plus fluoroquinolone. (c) need for additional antibiotics directed towards drug resistant or PES pathogens (d) need for antibiotics in patients with identified viral pathogen (e) optimal duration of treatment (f) addition of corticosteroids. Quinolones are preferred over macrolides if Legionella is suspected. With growing microbial resistance and continued need for appropriate coverage, several newer antibiotics have been studied in patients with CAP, with an ability to cover both typical, atypical and resistant CAP microbes, including newer generation cephalosporins, such as ceftaroline, ceftobiprole, ceftazidime-avibactam, and ceftolozane-tazobactam; newer macrolides like solithromycin; next generation fluoroquinolones like nemonoxacin zabofloxacin and delafloxacin; tetracyclines like omadacycline, and potent semisynthetic agents such as Lefamulin.
Severe community-acquired pneumonia: Current management and future therapeutic alternatives 2018 [6]	Cefotaxime or ceftriaxone are by far the most recommended β-lactams in sCAP. Combined therapy has been linked to a lower mortality in sCAP. Legionella pneumophila and gram-negative bacilli have been identified as risk factors associated with early failure in hospitalized patients with CAP. Fluoroquinolones exhibit a high activity against L. pneumophila even superior to older macrolides.

	Risk factors for sCAP caused by Gram-negative bacilli, including Pseudomonas aeruginosa, must be considered for selecting antimicrobials with high activity against these pathogens. In the empirical regimen, the substitution of a third-generation cephalosporin (cefotaxime or ceftriaxone) for an antipseudomonal β-lactam (piperacillin- tazobactam, cefepime, or meropenem) is judicious. Ceftaroline should be reserved for patients with microbiologically confirmed CAP due to penicillin-resistant S. pneumoniae (penicillin MIC ≥8 mg/L) or MRSA. Nevertheless, ceftaroline may be considered as a future option for empirical therapy in areas with high prevalence of MRSA or penicillin-resistant pneumococci and not be reserved exclusively for treatment failures. To date the use of corticosteroids in patients with severe CAP remains controversial and it is not recommended by the most recent guidelines. Delafloxacin has shown a good in vitro and in vivo activity against major pathogens associated with sCAP including Streptococcus pneumoniae and methicillin-resistant Staphylococcus aureus (MRSA). It is also highly active against Legionella spp. Zabofloxacin is another novel fluoroquinolone agent with potent activity against gram-positive pathogens including penicillin-resistant and levofloxacin resistant Streptococcus pneumoniae. Solithromycin is a novel macrolide with a potent in vitro activity against the most common pathogens, including macrolide-, penicillin-, and fluoroquinolone- Accepted Manuscript 8 resistant isolates of S. pneumoniae, as well as atypical bacterial pathogens. Solithromycin exhibits higher anti-inflammatory power than macrolides69, which may constitute an additional benefit for treatment of sCAP.
Recommendations and guidelines for the treatment of pneumonia in Taiwan 2019 [7]	Empirical antimicrobial therapy We used CRB-65 score and CURB-65 score to evaluate the severity of CAP in this guideline. Table 1 lists the recommended choices of antibiotics for empirical treatment of CAP. 2 No comorbidities, and no history of antibiotic treatment in the recent 3 months For patients without comorbidities and recent history of exposure to antimicrobial agents, monotherapy with a b-lactam

	antibiotic or a non-b-lactam drug for atypical pathogens (mainly for Mycoplasma or Chlamydophila infection), such as macrolides or tetracyclines, is recommended. The selection of antimicrobial agent depends on the patient's clinical manifestations and contact history. 3 With comorbidities, or history of antibiotic treatment in the recent 3 months For patients with comorbidities or recent history of exposure to antimicrobial agents, b-lactam monotherapy with or without addition of a macrolide are both optimal choices. Fluoroquinolones are listed as an alternative. Decision depends on the physician's clinical judgment, based on the individual patient's condition. Inpatient, non-intensive care unit (ICU) admission, with low severity (CURB-65 0-1) For patients admitted not primarily for the treatment of pneumonia, but for other medical concerns, e.g., multiple comorbidities, single elderly incapable of self-care, disabled patients who are unable to follow up at outpatient clinics, the recommended empirical antibiotics regimen is similar to those for the outpatient group. Intravenous antibiotics may be used for patients with gastrointestinal discomfort or malabsorption. Inpatient, non-ICU admission, with moderate severity (CURB-65 2-3) For CAP patients with moderate severity and CURB-65 score >= 2, we recommend combination therapy with a b-lactam antibiotic and a macrolide (1B). A fluoroquinolone (FQ) is listed as an alternative. Use of intravenous tigecycline is found to be associated with increased all-cause mortality compared to the control in a meta-analysis of phase III and IV clinical trials. The U.S. Food and Drug Administration issued a boxed warning to the tigecycline drug label. Consultation of an infectious disease specialist is recommended when considering tigecycline use. Inpatient, ICU admission, with high severity (CURB-65 4-5) For patients with high disease severity requiring ICU admission, we recommend combination therapy with a b-lactam plus either a macrolide or a FQ. In this group of patients, there is no good evidence to confirm which of these two combinations is more efficacious (2D).

Appendix C. MeSH Terms PubMed

Query	Filters	Search Details	Results
((((((((((((((((((Pneumonia[MeSH Terms]) OR (Pneumonias[Title/Abstract])) OR (Lobar Pneumonia[Title/Abstract])) OR (Lobar Pneumonias[Title/Abstract])) OR (Pneumonias, Lobar[Title/Abstract])) OR (Pneumonia, Lobar[Title/Abstract])) OR (Experimental Lung Inflammation[Title/Abstract])) OR (Experimental Lung Inflammations[Title/Abstract])) OR (Inflammation, Experimental Lung[Title/Abstract])) OR (Lung Inflammation, Experimental[Title/Abstract])) OR (Lung Inflammations, Experimental[Title/Abstract])) OR (Pneumonitis[Title/Abstract])) OR (Pneumonitides[Title/Abstract])) OR (Pulmonary Inflammation[Title/Abstract])) OR (Inflammation, Pulmonary[Title/Abstract])) OR (Inflammations, Pulmonary[Title/Abstract])) OR (Pulmonary Inflammations[Title/Abstract])) OR (Lung Inflammation[Title/Abstract])) OR (Inflammation, Lung[Title/Abstract])) OR (Inflammations, Lung[Title/Abstract])) OR (Lung Inflammations[Title/Abstract])	Guideline, in the last 5 years	("Pneumonia"[MeSH Terms] OR "Pneumonias"[Title/Abstract] OR "lobar pneumonia"[Title/Abstract] OR "lobar pneumonias"[Title/Abstract] OR (("Pneumonia"[MeSH Terms] OR "Pneumonia"[All Fields] OR "Pneumonias"[All Fields] OR "pneumoniae"[All Fields] OR "pneumoniae s"[All Fields]) AND "Lobar"[Title/Abstract]) OR "pneumonia lobar"[Title/Abstract] OR "experimental lung inflammation"[Title/Abstract] OR (("Experimental"[All Fields] OR "experimentally"[All Fields] OR "experimentals"[All Fields] OR "experimentation"[All Fields] OR "experimentations"[All Fields] OR "experimenter"[All Fields] OR "experimenter s"[All Fields] OR "experimenters"[All Fields]) AND "lung inflammations"[Title/Abstract]) OR (("Inflammation"[MeSH Terms] OR "Inflammation"[All Fields] OR "Inflammations"[All Fields] OR "inflammation s"[All Fields]) AND "experimental lung"[Title/Abstract]) OR "lung inflammation experimental"[Title/Abstract] OR (("Pneumonia"[MeSH Terms] OR "Pneumonia"[All Fields] OR ("Lung"[All Fields] AND "Inflammations"[All Fields]) OR "lung inflammations"[All Fields])	543

		AND "Experimental"[Title/Abstract]) OR "Pneumonitis"[Title/Abstract] OR "Pneumonitides"[Title/Abstract] OR "pulmonary inflammation"[Title/Abstract] OR "inflammation pulmonary"[Title/Abstract] OR "inflammations pulmonary"[Title/Abstract] OR "pulmonary inflammations"[Title/Abstract] OR "lung inflammation"[Title/Abstract] OR "inflammation lung"[Title/Abstract] OR "inflammations lung"[Title/Abstract] OR "lung inflammations"[Title/Abstract]) AND ((y_5[Filter]) AND (guideline[Filter]))	

Appendix D. Treatment Algorithm