



BRITISH COLUMBIA'S H1N1 PANDEMIC INFLUENZA RESPONSE PLAN (2009)

*Antibiotics for Secondary Pneumonia
in Community and Acute Care Settings*

Antibiotic Therapy Guidance
Clinical Care Advisory Group

October 19, 2009

TABLE OF CONTENTS

Acknowledgements.....	3
Preamble	4
Indication for Antibiotics for Secondary Pneumonia.....	4
Clinical Presentation of Suspected Secondary Pneumonia.....	5
CURB-65 and CRB-65 Scoring Systems.....	6
<i>Table 1: Adult empiric antibiotic guidance.</i>	8
<i>Table 2: Pediatric empiric antibiotic guidance.</i>	9
<i>Table 3: Recommended empiric dosing of oral (PO) antibiotics.</i>	10
<i>Table 4: Recommended empiric dosing of intravenous (IV) antibiotics.</i>	11
References.....	12

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- Pharmaceutical Services Division, Ministry of Health Services

This document is a companion to “Antibiotics for Secondary Pneumonia in Community and Acute Care Settings”, published October 2, 2009.

PREAMBLE

The risk of morbidity and mortality related to pneumonia secondary to pandemic (H1N1) 2009 influenza has prompted the development of specific antibiotic therapy guidance. The guidance in this document only applies to pneumonias secondary to pandemic (H1N1) 2009 influenza. Local resistance patterns should also help guide the choice of a specific antibiotic agent. Outside the pandemic scenario, clinicians are advised to follow their usual local guidance for treatment of pneumonia.

INDICATION FOR ANTIBIOTICS FOR SECONDARY PNEUMONIA (PROVEN OR SUSPECTED H1N1 INFECTION)

During the pandemic, antivirals will be used to treat ill patients with influenza. However, influenza infection may be associated with a number of pulmonary, cardiac, and hepatic complications which require hospitalization or outpatient treatment. A number of these complications are bacterial including pneumonia, sinusitis, and otitis media. Mortality is higher in patients who have secondary bacterial pneumonia post-influenza illness.

In individuals who have died with pneumonia in conjunction with pandemic (H1N1) 2009 influenza, the dominant pathogens identified are *Streptococcus pneumoniae*, Group A streptococci (and to a lesser extent other streptococci), *Staphylococcus aureus*, and *Haemophilus influenzae*. Note, in British Columbia, approximately 30% of *Staphylococcus aureus* is the aggressive strain of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA), and even in the absence of pandemic (H1N1) 2009 influenza there is an increasing number of adult and pediatric patients who are presenting with a primary MRSA pneumonia.

Hospitalized patients, particularly if they are in intensive care unit (ICU) settings, are at additional risk of acquiring infections from the hospital, particularly with *Staphylococcus aureus* (methicillin-sensitive *Staphylococcus aureus* [MSSA], hospital-acquired MRSA, or CA-MRSA), and resistant Gram negatives (often very resistant coliforms or *Pseudomonas aeruginosa*). In patients who are hospitalized with severe pneumonia, even if pandemic (H1N1) 2009 influenza is identified, it is usually impossible to exclude the presence of concurrent bacterial pneumonia. Microbiological diagnostic tests are usually not definitive in these patients, even if blood cultures or deep lung specimens are positive, because of the potential missed pathogen(s).

Empiric antibiotic therapy typically starts broad and becomes more focussed if and when a specific pathogen is identified. If there is no evidence of bacterial infection, the antibiotic

therapy may be stopped or made less broad. Conversely, patients whose pulmonary status worsens, particularly after several days in hospital on a ventilator, will likely require further broadening of antimicrobial therapy.

Guidance for when to give antibiotics for secondary bacterial pneumonia to patients with proven or suspected pandemic (H1N1) 2009 infection in specific care settings is as follows:

1. **Patients admitted to an ICU acute care setting:** Suggest that all receive antibiotics as part of their management.
2. **Patients admitted to an acute care setting (general hospital ward):**
 - a. If the reason for admission is moderate or severe influenza, most will likely receive antibiotics, particularly if there is a lobar infiltrate on chest X-ray or purulent sputum.
 - b. If the reason was primarily for social reasons, or management of dehydration or worsening of other organ systems rather than severity of pulmonary symptoms, antibiotics might not be needed, at least initially (case by case decision, subject to reassessment).
3. **Patients in a community care setting:** Most will likely not receive antibiotics initially.

CLINICAL PRESENTATION OF SUSPECTED SECONDARY PNEUMONIA

Clinical characteristics of adult, pregnant and non-pregnant, and pediatric patients who are not initially receiving antibiotics who have or may have a concurrent or superimposed bacterial pneumonia include the following:

- chest X-ray showing a lobar infiltrate or new infiltrates that develop after initial assessment (changes due to pandemic [H1N1] 2009 influenza have been reported to be patchy and bilateral rather than localized, but similar changes can be seen with bacterial infections, and with such findings it would be hard to exclude a bacterial infection);
- worsening respiratory symptoms (cough, shortness of breath, tachypnea, sputum amount, sputum purulence, bloody sputum, chest pain), respiratory clinical findings, gas exchange disturbances (oxygen saturation, CO₂ retention, acidosis);
- new onset or worsening fever, or persistent high fever beyond 3-5 days (if respiratory deterioration is not prominent, strongly consider other diagnostic possibilities and sources);
- new onset of unexplained drowsiness or confusion, hypotension or septic shock (if respiratory deterioration is not prominent, strongly consider other diagnostic possibilities and sources);

- persistence or new elevation of neutrophil count, or development of neutropenia (if respiratory deterioration is not prominent, strongly consider other diagnostic possibilities and sources);
- a “positive” sputum culture in the absence of the above types of findings will likely not be a useful guide.

The clinical presentation in pediatric patients with pandemic (H1N1) 2009 influenza warrants special mention. The most common presentations have been pneumonitis or bronchiolitis, but as many as 10% have presented with shock syndrome. Children presenting with shock require aggressive broad spectrum antibiotic coverage until a diagnosis of bacterial infection has been excluded.

The clinical evaluation of pregnant women with influenza-like illness requires evaluation of maternal and fetal status. For pregnant women with severe respiratory illness, consultation with physicians with expertise in both medical management of severe respiratory disease and an obstetrician is strongly suggested. Antibiotic choices should take into consideration the severity of illness and preferred antibiotics in pregnancy. It is usual to avoid doxycycline, and fluoroquinolones in pregnancy.

CURB-65 AND CRB-65 SCORING SYSTEMS

Scoring systems (clinical prediction rules) aid in determining the care setting for adult patients who have community acquired pneumonia. CURB-65 and CRB-65 are simple, validated schemes that allow clinicians to decide whether adult patients who have community acquired pneumonia (CAP) can be managed in the community, in hospital without ICU, or in hospital in ICU. They also predict mortality associated with CAP. It is not known how well CURB-65 and CRB-65 work for influenza, particularly because pandemic (H1N1) influenza tends to be less of an issue for elderly patients. Unlike some other more complicated scoring systems, CURB-65 and CRB-65 do not include underlying risk factors, which may be important in terms of outcome with H1N1 infection. **Like any such schemes they should only be used as a guide, with clinician impression of disease severity taking precedence.**

CURB-65 is named for each of the risk factors measured. *Each risk factor scores one point, for a maximum score of 5:*

- **C**onfusion (new onset)
- **U**rea greater than 7 mmol/L
- **R**espiratory rate of 30 breaths per minute or greater
- **B**lood pressure less than 90 mm Hg systolic or diastolic blood pressure less than or equal to 60 mmHg
- age **65** or older

Suggested management according to CURB-65 score:

- 0 to 1* consider community care setting
- 2 or 3* consider admission to acute care setting (general hospital ward)
- 4 or 5* consider admission to ICU acute care setting

CRB-65 is as above except it does not include a laboratory measure of renal function.

Suggested management according to CRB-65 score:

- 0* consider community care setting
- 1 or 2* consider admission to acute care setting (general hospital ward)
- 3 or 4* consider admission to ICU acute care setting

TABLE 1: ADULT EMPIRIC ANTIBIOTIC GUIDANCE FOR PNEUMONIA SECONDARY TO PANDEMIC (H1N1) 2009 INFLUENZA.

CARE SETTING		PATIENT POPULATION	PREFERRED ANTIBIOTIC(S)*	OTHER ALTERNATIVES*	COMMENTS †
Community	Community-acquired infection	Previously healthy, no antimicrobials in previous 3 months	<ul style="list-style-type: none"> doxycycline clarithromycin 	<ul style="list-style-type: none"> azithromycin OR erythromycin 	<ul style="list-style-type: none"> Of the macrolides, clarithromycin is preferred, as azithromycin may select out macrolide-resistant pneumococci and streptococci, and erythromycin has more gastrointestinal adverse effects
		Comorbidities** or antimicrobials in previous 3 months or residential care	<ul style="list-style-type: none"> Beta-lactam + doxycycline Beta-lactam + clarithromycin moxifloxacin 	<ul style="list-style-type: none"> Beta-lactam + azithromycin OR erythromycin levofloxacin high-dose 	<ul style="list-style-type: none"> Beta-lactam refers to amoxicillin high-dose, amoxicillin-clavulanate OR cefuroxime axetil The preferred fluoroquinolone is moxifloxacin, and levofloxacin high-dose should only be considered if moxifloxacin is not available (i.e., not on hospital formulary, etc.)
Acute		Non-ICU	<ul style="list-style-type: none"> Beta-lactam + doxycycline Beta-lactam + clarithromycin moxifloxacin 	<ul style="list-style-type: none"> Beta-lactam + azithromycin OR erythromycin levofloxacin high-dose 	<ul style="list-style-type: none"> Beta-lactam refers to amoxicillin high-dose, amoxicillin-clavulanate OR cefuroxime Vancomycin or linezolid should be considered with the initial empiric antibiotics if: patient is known to be colonized with MRSA; high prevalence of CA-MRSA; high prevalence of penicillin non-susceptible <i>S. pneumoniae</i> in the community
		ICU	<ul style="list-style-type: none"> Beta-lactam + azithromycin intravenous Beta-lactam + moxifloxacin 	<ul style="list-style-type: none"> Beta-lactam + levofloxacin high-dose 	<ul style="list-style-type: none"> Beta-lactam refers to cefotaxime, ceftriaxone, piperacillin-tazobactam, OR ticarcillin-clavulanate If strong history of penicillin allergy, tigecycline; OR ciprofloxacin + vancomycin; OR <i>if available</i>, moxifloxacin OR levofloxacin + aztreonam Vancomycin or linezolid should be considered with the initial empiric antibiotics if: patient is known to be colonized with MRSA; high prevalence of CA-MRSA; high prevalence of penicillin non-susceptible <i>S. pneumoniae</i> in the community
	Hospital-acquired infection	Non-ICU or ICU	<ul style="list-style-type: none"> imipenem-cilastatin OR meropenem + vancomycin 	<ul style="list-style-type: none"> piperacillin-tazobactam OR ticarcillin-clavulanate + vancomycin 	<ul style="list-style-type: none"> Empiric coverage if resistant Gram negatives suspected Choice of broad-spectrum agent is dependent on availability on formulary and local hospital coliform resistance patterns

* For recommended dosing, please see Tables 3 and 4.

** Comorbidities defined as: chronic lung disease (asthma, smoking, chronic obstructive pulmonary disease), diabetes, alcoholism, chronic renal or liver disease, heart failure, malnutrition or acute weight loss (>5%), hospitalization in past 3 months, lung cancer or other malignancies, immunosuppressing conditions like HIV/AIDS and asplenia or use of immunosuppressing drugs.

† For pregnant women with severe respiratory illness, consultation with physicians with expertise in medical management of severe respiratory disease and obstetrics may assist in choosing preferred antibiotic therapy.

TABLE 2: PEDIATRIC EMPIRIC ANTIBIOTIC GUIDANCE FOR PNEUMONIA SECONDARY TO PANDEMIC (H1N1) 2009 INFLUENZA.

CARE SETTING		PATIENT POPULATION	PREFERRED ANTIBIOTIC(S)*	COMMENTS
Community	Community-acquired infections	3 months to 15 years, mild illness	<ul style="list-style-type: none"> Not applicable 	<ul style="list-style-type: none"> Routine antibiotic use is <u>discouraged</u> for mild illness <u>not</u> requiring hospitalization, unless there is lobar disease and/or pleural effusion
		1 month to 5 years, moderate illness	<ul style="list-style-type: none"> Beta-lactam 	<ul style="list-style-type: none"> Beta-lactam refers to amoxicillin, amoxicillin high-dose OR cefuroxime axetil Choose amoxicillin high-dose if antimicrobials in previous 3 months or day care attendance If strong history of cephalosporin allergy, clarithromycin (rate of cross-reaction low if only penicillin allergy)
		5 to 15 years, moderate illness	<ul style="list-style-type: none"> Beta-lactam + clarithromycin** 	<ul style="list-style-type: none"> Beta-lactam refers to amoxicillin-clavulanate OR cefuroxime axetil
Acute	Non-ICU	1 month to 5 years, moderate illness	<ul style="list-style-type: none"> Beta-lactam 	<ul style="list-style-type: none"> For 1 to 3 months, beta-lactam refers to ampicillin, cefuroxime, OR cefotaxime as intravenous choices For 1 to 3 months, choose cefuroxime if antimicrobials in previous 3 months or day care attendance, but only if meningitis has been ruled out; otherwise, use cefotaxime For 3 months to 5 years, beta-lactam refers to cefuroxime as intravenous choice If strong history of cephalosporin allergy, clarithromycin (rate of cross-reaction low if only penicillin allergy) Vancomycin should be considered with the initial empiric antibiotics if: known colonization with MRSA; high prevalence of CA-MRSA; high prevalence of penicillin non-susceptible <i>S. pneumoniae</i> in the community
		5 to 15 years, moderate illness	<ul style="list-style-type: none"> Beta-lactam + clarithromycin** 	<ul style="list-style-type: none"> Beta-lactam refers to ampicillin OR cefuroxime as intravenous choices Vancomycin should be considered with the initial empiric antibiotics if: known colonization with MRSA; high prevalence of CA-MRSA; high prevalence of penicillin non-susceptible <i>S. pneumoniae</i> in the community
		1 month to 15 years, severe illness	<ul style="list-style-type: none"> vancomycin + cefotaxime +/- macrolide (e.g., clarithromycin) 	<ul style="list-style-type: none"> Non-influenza viral etiology is common in this age group Most children who become critically ill have co-morbidities including chronic lung disorders and immunodeficiency For critically ill children, vancomycin is recommended with the initial empiric antibiotics because of an increasing prevalences of CA-MRSA and penicillin non-susceptible <i>S. pneumoniae</i> in the community Macrolides (e.g., clarithromycin) are not indicated as initial therapy, but should be considered if there is a high suspicion of atypical bacterial pneumonia (based on local prevalence rates)
	Hospital-acquired infection	ICU or non-ICU, 3 months to 15 years, ventilated + non-ventilated (> 48 hours of hospitalization)	<ul style="list-style-type: none"> vancomycin + cefotaxime 	<ul style="list-style-type: none"> Coverage for <i>Pseudomonas</i> or other resistant Gram negatives should be guided by local bacteria prevalence rates and sensitivities

* For recommended dosing, please see Tables 3 and 4.

** While clarithromycin alone is recommended for standard community-acquired pneumonia in this age group, *S. aureus* and *S. pneumoniae* are the most commonly reported bacterial infections in the setting of pandemic (H1N1) 2009 influenza infection. Therefore, the addition of a beta-lactam is recommended.

TABLE 3: RECOMMENDED EMPIRIC DOSING OF ORAL (PO) ANTIBIOTICS FOR PNEUMONIA SECONDARY TO PANDEMIC (H1N1) 2009 INFLUENZA.

ANTIBIOTIC	USUAL ADULT DOSE	USUAL PEDIATRIC DOSE
amoxicillin high-dose	1 g PO TID	> 3 months old: 90 mg/kg/day PO divided TID (max 4 g/day)
amoxicillin	--	0 to 3 months old: 30 mg/kg/day PO divided BID (max 1500 mg/day) > 3 months old: 40 mg/kg/day PO divided TID (max 1500 mg/day)
amoxicillin-clavulanate	500 mg PO TID OR 875 mg PO BID	0 to 3 months old: 30 mg/kg/day PO divided BID (max 1750 mg/day) > 3 months old: 45 mg/kg/day PO divided BID to TID (max 1750 mg/day)
azithromycin	500 mg PO daily OR 500 mg PO 1 st dose, then 250 mg PO daily	> 1 month old: 10 mg/kg (max 500 mg) PO 1 st day, then 5 mg/kg PO daily (max 500 mg/day)
cefuroxime axetil	500 mg PO BID to TID	> 1 month old: 30 mg/kg/day PO divided BID (max 1 g/day)
clarithromycin	500 mg PO BID	> 1 month old: 15 mg/kg/day PO divided BID (max 1 g/day)
doxycycline	200 mg PO 1 st dose, then 100 mg PO BID	> 8 years old: 4 mg/kg/day PO divided BID (max 200 mg/day)
erythromycin	500 mg PO QID	> 1 month old: 40 mg/kg/day PO divided QID (max 4 g/day)
levofloxacin high-dose	750 mg PO Daily	--
linezolid	600 mg PO BID	--
moxifloxacin	400 mg PO Daily	--

TABLE 4: RECOMMENDED EMPIRIC DOSING OF INTRAVENOUS (IV) ANTIBIOTICS FOR PNEUMONIA SECONDARY TO PANDEMIC (H1N1) 2009 INFLUENZA.

ANTIBIOTIC	USUAL ADULT DOSE	USUAL PEDIATRIC DOSE
ampicillin	--	> 1 month old: 200 mg/kg/day IV divided Q6H (max 12 g/day)
azithromycin	500 mg IV Q24H OR 500 mg IV 1 st dose, then 250 mg IV Q24H	> 1 month old: 10 mg/kg (max 500 mg) IV 1 st day, then 5 mg/kg IV Q24H (max 500 mg/day)
aztreonam*	1 to 2 g IV Q8 to 12H	> 1 month old: 30 mg/kg IV Q6 to 8H (max 8 g/day)
cefotaxime	2 g IV Q8H	> 1 month old: 200 mg/kg/day IV divided Q6 to 8H (max 10-12 g/day)
ceftriaxone	2 g IV Q24H	> 1 month old: 100 mg/kg/day IV Q24H or divided Q12H (max 4 g/day)
cefuroxime	750 to 1500 mg IV Q8H	> 1 month old: 150 mg/kg/day (max 1.5 g per dose) IV divided Q8H
erythromycin	500 mg IV Q6H	> 1 month old: 40 mg/kg/day IV divided Q6H (max 4 g/day)
imipenem-cilastatin	500 mg IV Q6H	> 1 month: 100 mg/kg/day IV divided Q6H (max 500 mg Q6H)
levofloxacin high-dose	750 mg IV Q24H	--
linezolid	600 mg IV Q12H	--
meropenem	500 to 1000 mg IV Q8H	> 1 month: 60 mg/kg/day IV divided Q8H (max 6 g/day)
moxifloxacin	400 mg IV Q24H	--
piperacillin-tazobactam	3.375 g IV Q6H	> 1 month: 300 mg/kg/day of piperacillin IV divided Q6 to 8H (max 3 g piperacillin/dose Q6H)
ticarcillin-clavulanate	3.1 g IV Q6H	> 1 month: 300 mg/kg/day of ticarcillin IV divided Q4 to 6H (max 18 g ticarcillin/day)
tigecycline	100 mg IV, then 50 mg IV Q12H	--
vancomycin	25 mg/kg load, then 15 mg/kg IV Q8 to 12H (target trough 15-20 mg/L; also renal function dependent)	> 1 month: 60 mg/kg/day IV divided Q8H (target trough 10-15 mg/L; also renal function dependent)

*Aztreonam requires approval through the Special Access Program, Health Canada (telephone: 613-941-2108; fax: 613-941-3194; web: http://www.hc-sc.gc.ca/dhp-mps/alt_formats/hpfb-dgpsa/pdf/acces/sapfl_pasfl-eng.pdf).

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