INSTRUCTIONS FOR USE OF THE MARCiE REGISTERY

Registration

To use MARCiE you must submit an Application that can be accessed at https://www.fammed.wisc.edu/wren/resources/macrolides-for-asthma. Alternatively, you may contact the MARCiE Administrator, Dr, David L. Hahn MD MS. Dr. Hahn can be reached at <dlhahn@wisc.edu> or by cell at <608-234-3212>. To be registered as a MARCiE user, you will answer a few screening questions to verify (1) your status as a prescribing clinician who cares for adolescent and/or adult asthma patients, and (2) your interest in prescribing antibiotics for selected asthma patients. After providing your contact information you will be given the link to the MARCiE database, and you will be assigned a unique 3-digit CLINICIAN CODE that you must enter at each use.

Prospective Data Entry

MARCiE is designed for you to enter data on an individual patient at Baseline (when treatment is started), and periodically thereafter. To avoid "cherry picking" positive results, **you must enter Baseline data AT or BEFORE the time that antibiotic treatment is begun**. Thereafter you should enter follow up data on individual treated patients at approximately 3-month intervals up to 12-months post treatment initiation. If you do not have an office visit every three months with your MARCiE asthma patient, **you or your staff can obtain all follow up data over the phone**.

Linking Records Over Time for Individual Patients

This version of MARCiE does not automatically link individual patient records. To allow tracking, **you or your staff must enter the individual PATIENT CODE correctly** each time you enter data. At Baseline you will assign sequential numbers (001-999) to each patient you enter into MARCiE. You will then use the same PATIENT CODE each time you enter Follow Up data on that patient. **If you enter the incorrect PATIENT CODE, MARCiE will be unable to link patient records.** You will be provided with a MARCiE Patient Tracking Form that you can use to record the PATIENT CODE and associated patient contact information.

Exemption From Institutional Review Board (IRB) Oversight

The University of Wisconsin Institutional Review Board (IRB) has determined that your use of MARCiE is exempt from the need for written informed patient consent. This exemption classification is based on the assumption that you maintain patient anonymity. Do not share your Patient Tracking Form with the MARCiE administrator or any other individuals associated with the University of Wisconsin. Also, do not enter any patient identifiers into the MARCiE database, other than the general data on age, sex and smoking status.

DEFINITION OF TERMS

WELCOME PAGE

Clinician Code

Your unique 3-digit number (001 to 999) assigned to you when you register. Record this number on your copy of the MARCiE Patient Tracking Form.

Patient Code

The unique 3-digit number (001 to 999) you assign sequentially to each unique asthma patient you enter into MARCiE. On the Patient Tracking Form, enter patient identifying information next to the assigned patient code.

Baseline Data For A New Patient

Recorded once when beginning antibiotic treatment for asthma.

Follow Up Data for A Previously Entered Patient

Recorded multiple times after Baseline Data entry. The timing of Follow Up Data entry is flexible. Ideally it should occur every three months for one year.

DEFINITION OF TERMS

BASELINE ONLY

Basic Demographics

Patient age: Enter the age in years as of Today's Date.

Patient Sex: Enter patient sex as genetic sex, not as current gender identification. Check the Other category in rare cases of, e.g., Turner (full or partial loss of X chromosome) or Klinefelter (XXY) Syndromes.

Patient Smoking Status: Current Smoker: Smokes 1 or more cigarettes daily presently; Past Smoker: Smoked 1 or more cigarettes daily in the past, but not presently or in the last 6 months; Never smoker: Does not meet criteria for current or past smoking.

Asthma Classification

Severe refractory asthma: Asthma Control Test (ACT) score of 15 or less despite taking high dose inhaled corticosteroids (ICS) plus LABA or LAMA. For patients with ACT score of 15 or less without a trial of high dose ICS plus LABA or LAMA, see Other Asthma.

See Page 6 for details of the Asthma Control Test (ACT). See Page 7 for definition of high-dose inhaled corticosteroids (ICS) by brand.

New-Onset Asthma: First asthma symptoms (e.g., cough, wheeze, chest tightness, shortness of breath) began within the past 2 years. This term does not apply to adults with a history of childhood-onset asthma (COA) that remitted and then reappeared less than two years ago.

Other asthma: Asthma patients for whom you prescribe antibiotics who do not meet criteria above. This category includes severely uncontrolled asthma (ACT score ≤15) that cannot be classified as refractory.

Patient Reports that Asthma Began After an Acute Respiratory Illness: If the history is clearly positive or negative, answer accordingly. If the history is uncertain or unknown, answer "Unknown." (Lack of a clear history is common, especially for childhood-onset asthma. However, ~40% of patients with adult-onset asthma have answered positively to this question in primary care studies.)

Asthma Duration

Duration refers to the length of time between when the first asthma symptoms occurred and the present. Since the time of diagnosis is always later than the onset of first symptoms, estimate duration based on symptom onset, not time of diagnosis.

Asthma Confirmed by PFT-Evidence of Reversible Airway Obstruction?

Clinician-diagnosed asthma is sufficient to enter a patient into MARCiE. If you have pulmonary function test (PFT) data, please enter it here. Significant reversibility is defined as a change (either spontaneously or after treatment) in (1) FEV1%predicted of ≥12% and ≥200mL or (2) peak expiratory flow rate (PEFR) of ≥25% and ≥60 L/min.

FEVI%predicted: Forced Expiratory Volume in the first second, as the percent predicted from normal values. This value can be obtained by use of spirometry in any venue including patient use of a hand held spirometer.

PEFR: Peak Expiratory Flow Rate, as determined by a hand held peak flow meter in any venue (e.g., in the office or by the patient at home).

Lung Co Morbidities

Please record any additional lung disease diagnoses here. COPD, Emphysema and Chronic Bronchitis can be physician-diagnosed. You will be prompted to enter any available medical record data for PFT evidence for these conditions, if available (FEV1/FVC ratio, Diffusing Capacity of the Lungs for Carbon Monoxide - DLCO).

COPD: Irreversible airflow limitation defined by spirometry. You may enter physician-diagnosed COPD even if objective evidence for irreversible airflow limitation is not available. (COPD can occur with or without a smoking history; in fact 15% of men and 30% of women with COPD have never smoked).

Emphysema: Destruction of alveolar septa, with bleb creation, manifested by irreversible airflow obstruction, a typical "hyper inflated" chest wall deformity (increased AP diameter) and shortness of breath on exertion.

Chronic bronchitis: Chronic cough with phlegm production. The classic definition, derived from cohorts in Great Britain, is a productive cough that lasts at least three months, with recurring bouts occurring in two consecutive years.

Bronchiectasis: Abnormal widening of the bronchi or their branches, causing a risk of infection and exacerbations of respiratory difficulties. Enter this diagnosis if there is medical record evidence based on imaging studies.

Other: Enter a description of any other lung co morbidities that do not fit the previous categories.

Antibiotic Treatment for Asthma

The strongest evidence exists for azithromycin. Clarithromycin has been studied less extensively. The mechanism(s) of action for macrolide benefits for asthma are uncertain and could include anti-microbial and/or anti-inflammatory effects. Case report and clinical experience exists to support the use of tetracyclines (e.g. doxycycline, minocycline) but tetracyclines have not been studied in controlled trials.

Azithromycin. Accumulation within cells allows weekly dosing. Dosing above 600 milligrams weekly loads virtually all cells (including immune system cells) with 10x the MIC for *C. pneumoniae* (one possible etiologic agent). Azithromycin weekly doses used in most RCTs have been considerably higher than 600 milligrams, and were well tolerated. Consider prescribing 250 mgm tablets #40, 2 tablets (500 mgm) daily for 3 days (loading dose) followed by 3 tablets (750 mgm) once weekly x 11 weeks. The weekly dose may be given all at once, or in divided doses throughout the week. Once weekly (all at once) administration results in undetectable blood levels within 1-2 days, as the drug is trapped intracellularly.

Clarithromycin. Published RCTs have employed 500 milligrams twice daily for extended time periods with good clinical tolerability. Note that daily dosing results in sustained daily macrolide

blood levels, and epidemiologic studies find that clarithromycin carries a higher risk of cardiac adverse effects than azithromycin.

Doxycycline. A dose of 100 milligrams twice daily has been used clinically.

Minocycline. A dose of 100 milligrams twice daily has been used clinically.

DEFINITION OF TERMS

BASELINE AND FOLLOW UP

Asthma Control

Asthma Control Test (ACT) Score. The adult version of the ACT is an extensively validated 5-item questionnaire to measure asthma control in the prior 4 weeks in patients with asthma aged 12 years and above. A clinician, clinic team member and/or the patient can record the ACT. Access the adolescent and adult ACT at https://www.asthmacontroltest.com/ or download the PDF version displayed here at https://www.memphischildrens.org/Asthma_Control-12-and-older.pdf.

					SCORE
1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?					
All of the time **[1]**	Most of the time **[2]**	Some of the time **[3]**	A little of the time **[4]**	None of the time **[5]**	.....
2. During the past 4 weeks, how often have you had shortness of breath?					
More than Once a day **[1]**	Once a day **[2]**	3 to 6 times a week **[3]**	Once or twice a week **[4]**	Not at all **[5]**	.....
3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?					
4 or more nights a week **[1]**	2 to 3 nights a week **[2]**	Once a week **[3]**	Once or twice **[4]**	Not at all **[5]**	.....
4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?					
3 or more times per day **[1]**	1 to 2 times per day **[2]**	2 or 3 times per week **[3]**	Once a week or less **[4]**	Not at all **[5]**	.....
5. How would you rate your asthma control during the past 4 weeks?					
Not Controlled at All **[1]**	Poorly Controlled **[2]**	Somewhat Controlled **[3]**	Well Controlled **[4]**	Completely Controlled **[5]**	.....
				TOTAL:	.....

A Child version of the ACT (C-ACT) is available for use in children ages 5-11. The current version of MARCiE is not designed to record data on children, nor has the UW IRB reviewed or approved a protocol for entering data on children.

Date the ACT score was obtained. Enter the date on which the ACT score was obtained, as it may or may not be the same date as the data entry date ("Today's Date").

Asthma Exacerbations

The three following criteria are used by the National Institutes of Health (NIH) to define severe asthma exacerbations. Your patient may report these data to you. If desired, you can supplement patient reported history with a medical record review.

(1) ≥3 days of a steroid burst to manage worsening asthma symptoms. This could be an outpatient course of oral steroids prescribed or an outpatient course taken by your patient from a pre-existing prescription. You do not need to record here any inpatient oral or parenteral steroids taken during a hospitalization for asthma, as you will be recording hospitalizations below.

(2) Unscheduled Office or ER Visit for Worsening Asthma Symptoms This applies to any unscheduled or emergency visits for worsening asthma, whether or not your patient received a steroid burst. Note that both these two criteria could be recorded for the same exacerbation episode. That is why there is a final question in this section asking for the total number of discrete asthma exacerbations during the reporting time interval.

(3) Hospitalization for Asthma Record here only those hospitalizations that were for treatment of worsening asthma. Enter hospitalizations - believed caused by antibiotic treatment side effects or adverse events - under **Side Effects/Adverse Events** later in this section.

Total number of discrete asthma exacerbations Because a single exacerbation could encompass all three of the above criteria, it is important to enter the total number of discrete exacerbations here. For example, a patient might visit her doctor for worsening symptoms and have her inhaled steroids doubled (criterion 2), call in the next day and be prescribed a steroid burst over the phone (criterion 1) and be hospitalized the next week for intractable symptoms (criterion 3). This pattern represents a single exacerbation episode, even though all three individual criteria are present.

Asthma Medications, Currently Taking

The aim here is to record the controller medications that your patient is currently taking. Record what your patient is actually taking, if different from what was prescribed. If there has been a recent change, record the most recent medication information.

Inhaled corticosteroids (ICS). Refer to this chart from the Global Initiative for Asthma (GINA) Guideline to determine Low, Medium or High **daily dose** categories for adults and adolescents.

Inhaled corticosteroid	**Adults and adolescents**		
	Low	**Medium**	**High**
Beclometasone dipropionate (CFC)*	200-500	>500-1000	>1000
Beclometasone dipropionate (HFA)	100-200	>200-400	>400
Budesonide (DPI)	200-400	>400-800	>800
Ciclesonide (HFA)	80-160	>160-320	>320
Fluticasone furoate (DPI)	100	NA	200
Fluticasone propionate (DPI)	100-250	>250-500	>500
Fluticasone propionate (HFA)	100-250	>250-500	>500
Mometasone furoate	110-220	>220-440	>440
Triamcinolone acetonide	400-1000	>100-2000	>2000

Doses are in mcg. CFC: chlorofluorocarbon propellant; DPI: dry powder inhaler; HFA: hydrofluoroalkane propellant. *Included for comparison with older literature.

For new preparations, the manufacturer's information should be reviewed carefully, as products containing the same molecule may not be clinically equivalent.

Oral Corticosteroids (OCs). Check this box if OCs are prescribed on a regular basis (either daily or every other day). Do not check this box if OCs were given only during exacerbations.

Long-Acting Beta-Adrenoceptor Agonist (LABA). LABAs include salmeterol (Serevent Diskus), formoterol (Perforomist), arformeterol (Brovana), or in combination with an inhaled steroid (e.g., Advair, Symbicort). Note that the FDA recommends that LABAs should be used ONLY in conjunction with inhaled steroids.

Long-Acting Muscarinic Antagonist (LAMA). LAMAs include tiotropium (HandiHaler, Respimat), aclidimium (Genuair), glycopyrronium (Breezhaler), umeclidinium (Ellipta).

Biologic. Biologics include omalizumab (Xolair), mepolizumab (Nucala), reslizumab (Cinquir), benralizumab (Fasenra), dupilumab (Dupixent.

Other. Other agents include leukotriene modifiers, cromolyn sodium, theophylline.

Follow up on antibiotic treatment for asthma

The following two questions are aimed at determining whether the antibiotic you prescribed for asthma was actually taken.

Did your patient begin the prescribed antibiotic(s)? If your patient did not begin taking your prescription, please indicate why in the text box.

Has your patient completed the prescribed duration of antibiotic(s)? If your patient has not completed the prescribed duration of antibiotics, please indicate why in the text box, e.g., "discontinued due to side effects", "medication refilled and still taking", "switched to a different antibiotic (indicate drug and dose)." At the 3-month data collection, this question refers to the initial (baseline) prescription. At the 6-month data collection and beyond, this question refers to any subsequent extensions (refills) or newly prescribed antibiotics for asthma. If you did not prescribe any subsequent extensions (refills) or new antibiotics for asthma, check "Not Applicable."

Side Effects/Adverse Events

The following two questions are aimed at determining whether the antibiotic you prescribed for asthma was associated with any side effects or adverse events. Check "Not Applicable" if you completed this question in a previous survey, and your patient is no longer taking antibiotics for asthma.

Has your patient experienced any side effects while taking the antibiotic(s)? The definition of a drug side effect is a secondary, typically undesirable effect of a drug. You may record multiple side effects as needed. Record only side effects that you believe are attributable to the antibiotic treatment for asthma.

Has your patient experienced any adverse events while taking the antibiotic(s)? The definition of an adverse drug event is a negative consequence of the drug that results in unintended injury or illness that may or may not have been preventable. You may record multiple adverse events as needed. Record only adverse events that you believe are attributable to the antibiotic treatment for asthma.