

575 **ON LINE REPOSITORY**

576 **Allergy skin testing**

577 Skin testing was performed by the prick puncture method on the volar surface of the forearm
578 using a Multi-Test II device (Lincoln Diagnostics, Decatur, IL). Allergen extracts (mouse
579 epithelia, dog epithelia, *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, cat hair,
580 rat epithelia, American and German cockroach mix, German cockroach, *Alternaria tenuis*,
581 *Cladosporium herbarum*, *Aspergillus* mix, *Penicillium notatum*, Ragweed mix, and Timothy
582 grass) were obtained from Greer Laboratories (Lenoir, NC). All extracts were 1:20 (wt/vol)
583 except for *D. farinae*, *D. pteronyssinus*, Timothy grass, and cat, which were standardized
584 extracts of 10,000 Biologic Allergy Units per ml. The resulting wheals were measured after 15
585 minutes. Wheal sizes were calculated as the average of the longest diameter and its orthogonal
586 midpoint diameter. Skin tests were considered valid if the wheal size of the negative control
587 (50% Glycerin, 50% Coca's solution) was 3 mm or smaller and the wheal size of the positive
588 control (histamine) was at least 3 mm larger than the wheal size of the negative control. A skin
589 test response was considered to be positive if the wheal size for the allergen was at least 3 mm
590 larger than that for the negative control.

591

592 **Assessing control level**

593 Table 1e below shows the levels of symptoms, medication use and pulmonary function that
594 determine the four possible asthma control levels.

595

596 **Table 1e. Control Levels of Symptoms, Bronchodilator Usage, FEV₁, and Exhaled Nitric**

597 **Oxide (FENO) ***

598	<u>Symptoms</u> [†]				
599	<u>Control Level</u>	<u>Days</u>	<u>Nights</u>	<u>FEV₁ (% best) ‡</u>	<u>FE_{NO} §</u>
600	1	0 – 3	0 – 1	≥ 80	0 – 20
601	2	4 – 9	2	≥ 80	20.1 – 30
602	3	10 – 13	3 – 4	70 – 79	30.1 – 40
603	4	14	5 – 14	< 70	> 40

604 * The overall control level was determined by the highest value among the individual
 605 components of control—days, nights, FEV₁.

606 † Determined from participant recall, based on the 2-week interval directly preceding the study
 607 visit. Days of symptoms is defined as the maximum of either the number of days with asthma
 608 symptoms in the last two weeks or the number of days of rescue albuterol use. Nights of
 609 symptoms is defined as the maximum number of either the number of nights of awakenings due
 610 to asthma sleep disruptions or nights of albuterol use after awakening due to asthma.

611 ‡ FEV₁ (% best) is calculated by dividing the current visit FEV₁ by the best FEV₁ from all
 612 previous visits.

613 § Applied to FE_{NO} group only.

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614 **Adjusting medications**

615 Table 2e shows the escalating treatment steps that could be employed by the study physicians.

616

617 **Table 2e: Treatment Steps For Controller Medications**

618 **Step Medication**

619 0 No controller medication; albuterol prn

620 1 Fluticasone DPI 100 mcg qd

621 2 Fluticasone DPI 100 mcg bid

622 3 Fluticasone 100 mcg / salmeterol 50 mcg bid

623 4 Fluticasone 250 mcg / salmeterol 50 mcg bid

624 5 Fluticasone 500 mcg/ salmeterol 50 mcg bid

625 6 Fluticasone 500 mcg/ salmeterol 50 mcg bid + either low dose theophylline or
626 montelukast qd

627

628 **Masking procedure**

629 The unblinded study coordinator selected the appropriate treatment step from the computer

630 algorithm generated recommendations depending upon treatment group assignment and FE_{NO}

631 level. The study coordinator gave a copy of the selected treatment to the asthma counselor, who

632 reviewed the treatment plan, reinforced adherence, and provided environmental control

633 education to the participant. With the exception of the ACE study coordinator, all other research

634 site personnel were blinded to ACE treatment group assignments.

635

635 **Treatment Step Adjustment**

636 Table 3e below demonstrates how treatment was adjusted based on control level when adherence
637 was at least 50%. Treatment level was lowered one step when participants were under good
638 control (level 1) for two consecutive visits. Due to the common increase in asthma symptoms
639 expected in September no treatment reductions occurred in August. Treatment could be
640 increased one, two or three steps for lack of control, but not beyond Step 6, the highest treatment
641 step. When control was poor (level 4), physicians had the option of either increasing treatment
642 three steps or increasing two steps and adding a prednisone course.

643

644 When adherence was less than 50%, treatment was only increased if the current treatment step
645 was inadequate for the current control level. At control levels 2 and 3, treatment step 2 was
646 prescribed, if the participant was currently on a lower treatment step. At control level 4, a
647 prednisone course was prescribed. Treatment was also increased to Step 3, if the participant was
648 currently on a lower step.

649

650 **Table 3e. Treatment Step Adjustment Based on Control Level**

651 <u>Control Level</u>	<u>Step Level Change</u>
652 1	No change, or decrease 1 step
653 2	Increase 1 step
654 3	Increase 2 steps
655 4	Increase 3 steps or 2 steps plus prednisone

656

656 **Table 4e. Allergic and Inflammatory Biomarkers by Study Group at Randomization***

657		FE_{NO} Group	Reference Group
658		(n=276)	(n=270)
659	Total IgE (kU/L)	240 (93 – 642)	294 (102 – 695)
660	Allergen specific IgE (kU _A /L) *		
661	<i>Alternaria tenuis</i>	0.13 (0.05 – 3.17)	0.12 (0.05 – 6.03)
662	Cat	0.30 (0.05 – 6.85)	0.48 (0.05 – 6.55)
663	<i>D. pteronyssinus</i>	0.24 (0.05 – 1.78)	0.40 (0.05 – 6.19)
664	<i>D. farinae</i>	0.20 (0.05 – 1.98)	0.40 (0.05 – 5.57)
665	German cockroach	0.21 (0.05 – 3.66)	0.38 (0.05 – 5.76)
666	Sum of the five allergen specific IgEs	14.6 (1.1 – 45.8)	19.1 (2.8 – 52.9)
667	Number of positive skin tests †	4.8 ± 3.5	4.8 ± 3.2
668	Skin test sensitivity, % positive		
669	Cat	57.5 (153/266)	58.9 (156/255)
670	Dog	14.7 (39/266)	12.8 (34/265)
671	Dust mite	46.2 (123/266)	47.5 (126/265)
672	Mold	52.6 (140/266)	50.6 (134/265)
673	Cockroach	60.5 (161/266)	61.9 (164/265)
674	Rodent	38.3 (102/266)	38.1 (101/265)
675	Allergen Exposure ‡		
676	Cat – Fel d 1 (µg/g)	4.37 (1.29 – 23.72)	4.01 (1.43 – 17.88)
677	Dog – Can f 1 (µg/g)	3.38 (0.97 – 36.75)	3.40 (0.84 – 25.77)
678	Dust mite – Der p 1 (µg/g)	0.20 (0.20 – 0.20)	0.20 (0.20 – 0.20)

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679	Dust mite – Der f 1 (µg/g)	1.44 (0.16 – 9.82)	0.99 (0.16 – 7.66)
680	Cockroach – Bla g 1 (U/g)	0.50 (0.50 – 1.40)	0.50 (0.50 – 2.85)
681	Mouse – Mus m 1 (µg/g)	0.61 (0.12 – 4.32)	0.81 (0.15 – 5.50)
682	Blood eosinophils (per µl)	211 (112 – 380)	213 (126 – 370)
683	Sputum eosinophils (% of WBC)	0.95 (0 – 2.75)	0.90 (0 – 1.60)
684	Methacholine PC ₂₀ (mg/ml) §	3.56 (0.63 – 25)	3.13 (0.97 – 26)

685

686 Plus-minus values are means ± SD. Interquartile range is provided in parentheses with medians.

687 Counts are provided in parentheses with percentages. Sputum eosinophils and methacholine
688 challenge were conducted at four sites only.

689 * Half the lower limit of detection was 0.05 kU_A/L for all allergen specific IgEs.

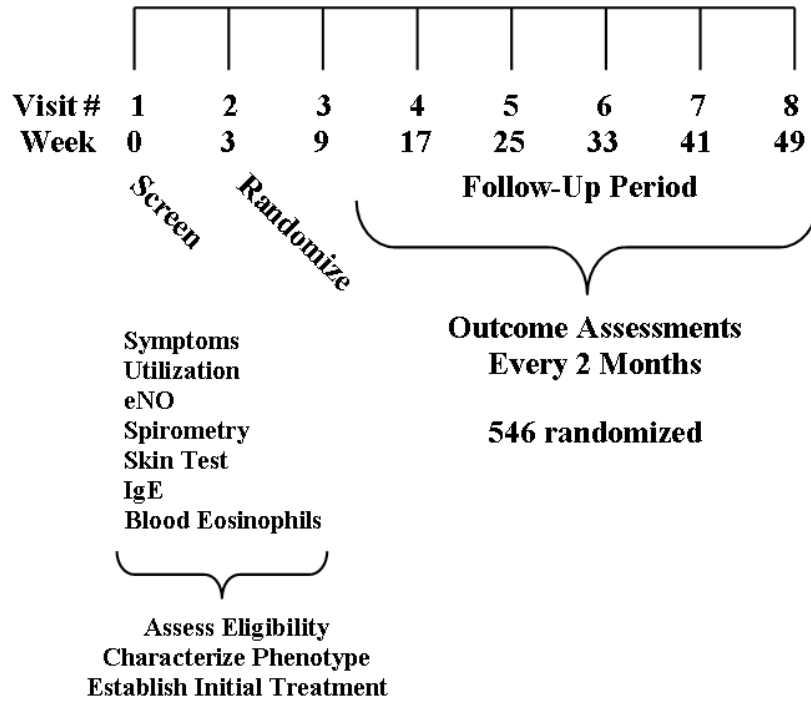
690 † Skin test positive includes *D. pteronyssinus* or *D. farinae* for dust mite, *Alternaria tenuis*,
691 *Cladosporium herbarum*, *Aspergillus* mix, or *Penicillium notatum* for mold, American and
692 German cockroach mix or German cockroach for cockroach, and mouse or rat epithelia for
693 rodent.

694 ‡ Lower limit of detection was half of 0.61, 0.32, 0.39, 0.32, 1.0 and 0.042 for cat, dog, *D.*
695 *pteronyssinus*, *D. farinae*, cockroach and mouse, respectively.

696 § Individuals that did not reach PC₂₀ were assigned an upper limit of detection (26 mg/ml).

697 **Figure 1e. Study Schema**

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