PROGNOSIS IN CHILDREN WITH OTITIS MEDIA WITH EFFUSION

by

Joshua Titmus

BA, Duquesne University, 2003

Submitted to the Graduate Faculty of

Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2007

UNIVERSITY OF PITTSBURGH

Graduate School of Public Health

This thesis was presented

By

Joshua Titmus

It was defended on

December 19, 2007

and approved by

Thesis Advisor:
Roslyn A. Stone, Ph.D
Associate Professor
Department of Biostatistics
Graduate School of Public Health
University of Pittsburgh

Committee Member:
Ellen M. Mandel, M.D.
Associate Professor
Department of Otolaryngology
School of Medicine
University of Pittsburgh

Committee Member:
Howard E. Rockette, Ph.D
Professor and Chair
Department of Biostatistics
Graduate School of Public Health
University of Pittsburgh

Committee Member:
John W. Wilson, Ph.D
Assistant Professor
Department of Biostatistics
Graduate School of Public Health
University of Pittsburgh

Copyright © by Joshua Titmus

2007

PROGNOSIS IN CHILDREN WITH OTITIS MEDIA WITH EFFUSION

Joshua Titmus, M.S.

University of Pittsburgh, 2007

The public health significance of this study is to provide researchers and clinicians interested in the study and treatment of Otitis Media with effusion (OME) with a better understanding of the associations between covariates and antibiotic treatment with the resolution of OME, which in turn will inform the decision-to-treat process. In a secondary analysis of the data from a series of three efficacy trials, we focus on the roles of laterality (unilateral vs. bilateral disease) and sidedness (right vs. left ear) as prognostic factors. The D&A trial compared the efficacy of decongestant and antihistamine (D/A) to placebo, the ABI trial was similar but compared amoxicillin (with and without to D/A) to placebo, and the ABII trial compared the efficacy of 2 promising antibiotics to amoxicillin. Each trial assessed subjects for OME at baseline, 2 weeks, and 4 weeks.

The prevalence of OME at each time point was described by laterality and sidedness. McNemar's test showed no evidence that left and right ears differ with respect to prevalence rates at 2 or 4 weeks (OR = 1.106 and OR = 0.858, respectively). Transition matrices of changes in OME status from 0 to 2 weeks and 2 to 4 weeks described the dependence of prior effusion status on a subject's current OME status. Multinomial regression was used to assess baseline covariates associated with prevalence and transitions of effusion status at each time point. We identified statistically significant prognostic factors of OME, including duration of effusion. Our analyses showed no differences in either prevalence of OME or in transitions of effusion status attributable to sidedness. A Chi Square Goodness-of-Fit test at each timepoint rejected the hypothesis of independence, $p < 0.001$. An ear-level GEE analysis demonstrated that effusion status of a contralateral ear was a significant predictor of effusion in the other ear ($OR = 1.44$, $p < 0.001$). There was no significant effect of sidedness ($p = 0.86$) and bilateral disease does not resolve at the rate predicted by unilateral resolution. This reanalysis using correlated data methods augments the initial findings by further examining sidedness and documenting transitions over time.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1.0 INTRODUCTION

Otitis media (OM) is one of the most common childhood infections, the second most common diagnosis made by pediatricians at sick patient visits, and the leading cause of physician visits by children; costs in the United States alone are estimated to be 3 to 5 billion dollars annually (Rovers, 2004). In light of the fact that antibiotics and surgery have only moderate efficacy for OM and because antibiotics present an associated risk that may outweigh the potential benefit, management of OM, in general, remains controversial (Glasziou, 2002).

Otitis media with effusion (OME) is particularly difficult in terms of the questions regarding the decision to treat because it represents a stage of OM that is different than acute otitis media (AOM), one absent the signs, symptoms, and some of the associated threats of an acute infection (Daly, 1999). OME also is characterized by a high rate of spontaneous recovery. Because of increasing antibiotic resistance and the call for judicious use of antibiotics, antibiotics are not recommended for routine treatment of OME. In actuality only the most severe manifestations of OME need to be treated. However, due to the convoluted nature of the disease, prediction of the onset and resolution of the disease have proven difficult over the years. Despite the general interest of the scientific community and advances in all areas of the study of OM, evidenced by the increasing number of publications listed on PubMed (from 250 in 1967 to 740 in 2005), much of the disease's etiology and pathogenesis remains uncertain (Rovers, 2004). An investigation of the influence of specific covariates may contribute to a better overall understanding of OME, which, in turn, could inform the decision-making process.

1.1 REVIEW OF LITERATURE

1.1.1 The Nature of OME

OM is a multi-factorial disease that has stages of severity and variant viral and bacteriological intensity over time (Tran, 2005). Due to the absence of many of the more obvious symptoms of AOM, which make it easier to define clearly and observe an outcome of interest, future investigations into OME may need to take better care to account of the stages of disease, its clinical course, and, most importantly for our purposes, the context under which the various manifestations occur, i.e. the variables that relate to a particular expression of the disease and that may influence outcome.

1.1.2 Prognostic Factors and OME

Several covariates have been found to be statistically significant predictors of outcome in efficacy trials of pharmacological treatments for OME. Mandel et al., over the course of the three studies that provide the data for the present investigation, showed varying degrees of efficacy of the treatments under study. Laterality of OME (unilateral versus bilateral) was the most significant predictor of resolution of effusion, with bilateral cases taking longer to resolve.

1.1.3 Laterality

Because laterality of disease is commonly acknowledged to be related to disease severity, it is one of the most important prognostic variables to consider in the diagnosis and proper management of OME. Bilaterality, in particular, has been reported to be one of the most important risk factors in chronic OME and has been understood to reflect a "more difficult disease process than a unilateral one" (Jero, 1997a). Some clinical investigators believe that bilateral and unilateral cases of OME represent different manifestations of the disease, i.e. whether the disease is systemic, or, contrarily, whether specific local factors of individual ears, such as Eustacian tube dysfunction, contribute independently to the development of the condition in a child (van Heerbeek, 2003). By contrast, even if a bilateral ear were the same, biologically, as a unilateral ear and had the same probability of becoming effusion-free, we would expect a child with bilateral disease to have a lesser chance of becoming effusion-free in a specified time interval simply because there are two affected ears. Laterality is a controversial topic in the study of OME.

1.2 DESCRIPTION OF THE ORIGINAL STUDIES

The data are taken from a series of efficacy studies conducted at the Children's Hospital of Pittsburgh between July 1, 1978 and December 31, 1987. Infants and children from seven months to 12 years of age with suspected OME were referred to the studies from the ambulatory care center of the hospital and from private practices throughout the surrounding community.

1.2.1 Decongestant and Antihistamine (D & A) Trial (Cantekin et al., 1983)

Six hundred eleven children were enrolled in the study, which took place between July 1, 1978 and June 30, 1981. Five hundred fifty-three children (91%) completed the study. Of the 553 subjects. 393 (71%) had bilateral OME at entry; the remaining 160 (29%) had unilateral disease (10 of these 160 had to be excluded at the 4-week follow-up because one ear could not be checked satisfactorily). The investigators compared the efficacy of a 4-week course of an oral decongestant-antihistamine (D/A) combination with that of a placebo.

Children were evaluated at 2 weeks and again at 4 weeks for the presence or absence of middle-ear effusion (MEE). MEE is commonly the endpoint of interest in studies of OME, since its presence is often associated with the inflammation of the middle ear indicative of the disease.

The study concluded that the standard D/A treatment was not efficacious relative to placebo. The p-values were 0.74 for subjects with unilateral disease at entry and 0.67 for subjects who had bilateral disease at entry. When treatment and placebo groups were compared in regard to the proportions who had bilateral, unilateral, or no effusion at the 4-week endpoint, no statistically significant difference was observed for either the unilateral or bilateral groups ($p = 0.51$ and $p = 0.38$, respectively). Comparisons made within each treatment group showed that those children who had unilateral effusion at entry were twice as likely to become effusion-free as those who had entered with bilateral effusion (30 of 80 [37.5%] compared to 36 of 195 [18.5%] for the placebo group and 27 of 80 [33.8%] compared to 41 of 198 [10.3%] for the D/A treatment group; $p < 0.001$) and those children who had had bilateral effusion at entry were three times as likely to have experienced bilateral effusion at 4 weeks (32 of 160 [20%] compared to 247 of 393 [62.9%] unilateral children).

Subject characteristics such as age, previous use of antimicrobials, duration of effusion, sex, race, socioeconomic status, season at entry, upper-respiratory-tract infection, history of middle-ear disease, diagnosed allergy, and adenoid size were balanced over all treatment groups. None of these variables appeared to diminish the efficacy of the drug relative to that of the placebo. No interactions between treatments and the stratification variables (age, previous use of antimicrobials, and duration of effusion) were identified when the data were analyzed using logistic regression. In addition to laterality, duration of effusion and prior history of OM appeared to be related to effusion at the 4-week timepoint ($p < 0.05$), as did a time-dependent covariate, upper-respiratory-tract infection ($p < 0.01$). Of the subjects with unilateral disease at entry, the proportion who were effusion-free at 4 weeks was twice that of subjects who had had bilateral disease at entry (57 of 160 [35.6%] and 77 of 393 [19.6%]).

1.2.2 Antibiotic (AB) I Trial (Mandel et al., 1987)

Five hundred eighteen children with OME, of whom 148 were unilateral and 326 were bilateral, were enrolled in the study between July 1, 1981 and October 30, 1984. The investigators compared the efficacy of a 2-week course of amoxicillin, with and without a 4-week course of an oral D/A combination, with that of placebo (two separate placebo groups, one for antibiotic and one for D/A).

Children were evaluated at 2-week and 4-week endpoints for the presence or absence of MEE. Of the 488 children who entered the study, 94% were evaluated at the 2-week timepoint, 4-week timepoint, or both. The rate of resolution of MEE of the 474 children who were observed at the 4-week endpoint was twice as high in those treated with amoxicillin, either with or without the D/A, compared to those who received the placebo (50 of 158 [31.7%] in amoxicillin and D/A; 46 of 160 [28.8%] in amoxicillin/placebo; and 22 of 156 [14.1%] in placebo/placebo, $p < 0.001$). Outcomes were consistently better in children who received amoxicillin. The investigators concluded that amoxicillin treatment increased the likelihood of resolution of MEE to some extent.

Subject characteristics such as age, previous use of antimicrobials, duration of effusion at entry, sex, race, laterality of MEE, season at entry, upper-respiratory-tract infection, history of middle-ear disease, allergy diagnosed, and socioeconomic status appeared balanced over the treatment groups. No statistically significant interaction between the treatment and any of these variables was identified using logistic regression methods. Among both the amoxicillin-treated subjects and placebo-treated subjects, resolution was more likely in those who entered the study with unilateral effusion, those who had had effusion for eight weeks or less, and those without an upper-respiratory-tract infection at the 4-week timepoint. As in the D & A trial, laterality of disease was the strongest prognostic variable ($p < 0.001$). Subjects with unilateral effusion at entry were nearly twice as likely to have no effusion at 4 weeks as those who had entered the study with bilateral effusion.

1.2.3 AB II Trial (Mandel *et al.*, 1991)

Three hundred thirty-one children were enrolled in the study, of whom 85 (26%) were unilateral and 246 (74%) were bilateral, between July 1, 1984 and December 31, 1987. Three hundred fourteen (95%) children were evaluated at the 2-week timepoint and 310 (94%) were evaluated at the 4-week timepoint. The investigators were interested in whether either erythromycin-sulfisoxazole (E-S) or cefaclor, both “second-line” antibiotics, would have greater short-term efficacy than that found for amoxicillin in the original AB trial.

The trial was terminated early due to an interim analysis conducted after half of the estimated number of children required for the trial had reached both the 2-week and 4-week timepoints. At that time, the two treatments hypothesized to be more efficacious than amoxicillin were actually less so, as indicated by the study's primary outcome measure of the proportions of children who were effusion-free at the 2-week and 4-week endpoints. It was determined that the likelihood of detecting "true" differences between the treatments in the direction hypothesized *a priori* was not sufficient to continue subject accrual. Though not the original intent of the trial, the researchers regarded the results of the amoxicillin versus placebo comparisons of the present study a valuable continuation of the data gathered in the previous AB trial. Amoxicillin continued to show promise in terms of its efficacy relative to placebo.

Subject characteristics such as age, sex, race, previous middle-ear disease, laterality, duration of effusion, speech-recognition threshold (SRT) in worse ear, season at entry, upper-respiratory-tract infection, allergy diagnosed, parent with history of ear disease, and occupation of primary wage earner were included in logistic models to ascertain their association with prognosis and whether statistical interaction with treatment was evident. In no case were the results of the analysis of primary endpoints of the trial substantially altered by adjustment for any of these variables. The percentages of subjects who were effusion-free at both the 2-week and 4-week timepoints were lower in children with bilateral effusion, in those with SRT greater than or equal to 25 dB HL in at least one ear at entry (compared to those who had SRT < 25 dB HL bilaterally), and in females. Interaction between sex and SRT may explain the poorer outcome in females.

Table 1 summarizes the number of evaluated subjects at baseline, 2 weeks, and 4 weeks by study, laterality, and treatment group in these three trials. In most subgroups, at least 90% of the subjects were followed at the 2 week and 4 week timepoints.

Table 1. Number of Subjects by Study, Laterality, and Treatment

Study	Treatment	Laterality of OME at entry	Baseline	2 Week Observed		4 Week Observed	
				N	%	N	%
D & A	Placebo (N=302)	Unilateral R	40	36	90	38	95
		Unilateral L	43	39	91	39	91
		Bilateral	219	202	92	197	90
	D&A (N=306)	Unilateral R	39	36	92	35	90
		Unilateral L	52	45	87	43	83
		Bilateral	215	206	96	199	93
AB I	Amoxicillin (N=167)	Unilateral R	26	24	92	24	92
		Unilateral L	31	29	94	29	94
		Bilateral	110	104	95	106	96
	Placebo (N=169)	Unilateral R	23	22	96	22	96
		Unilateral L	19	17	89	18	95
		Bilateral	127	111	87	113	89
	Amox / D&A (N=174)	Unilateral R	30	25	83	24	80
		Unilateral L	27	24	89	24	89
		Bilateral	117	110	94	107	91
AB II	Amoxicillin (N=82)	Unilateral R	8	7	88	7	88
		Unilateral L	12	11	92	10	83
		Bilateral	62	60	97	59	95
	Placebo (N=81)	Unilateral R	12	12	100	11	92
		Unilateral L	8	8	100	8	100
		Bilateral	61	58	95	56	92
	E-S (N=84)	Unilateral R	14	12	86	11	79
		Unilateral L	9	8	89	8	89
		Bilateral	61	60	98	61	100
	Cefaclor (N=83)	Unilateral R	10	9	90	10	100
		Unilateral L	11	9	82	9	82
		Bilateral	62	59	95	59	95

1.3 STUDY DESIGNS

All studies were approved by the Human Rights Committee of the Children's Hospital of Pittsburgh and written informed consent was obtained for all subjects. In each of these three studies, a careful preliminary examination, which included a standardized history for each subject and the findings of a standardized ear, nose, and throat examination, including a detailed description of observations on pneumatic otoscopy, was conducted after subjects met specific eligibility requirements. Subjects were deemed ineligible if they had any of the following:

D & A Trial: congenital craniofacial malformations; Down's syndrome; systemic illnesses such as asthma, cystic fibrosis, or diabetes mellitus; a history of tonsillectomy, adenoidectomy, or tympanostomy-tube insertion; a structural middle-ear abnormality such as tympanic-membrane perforation or adhesive OM; a sensorineural hearing loss or a conductive loss not attributable to the middle-ear effusion; severe upper-airway obstruction; acute suppurative otitis media; purulent rhinitis; acute or chronic sinusitis: or a history of having received sympathomimetic amines or antihistamines during the preceding 30 days.

AB I Trial: same as the D & A trial but also history of hypersensitivity to any form of penicillin.

AB II Trial: same as the AB I trial but also hypersensitivity to erythromycin, sulfonamides or cephalosporins.

Subjects who met the selection criteria were stratified according to age (7 to 23 months, 2 to 5 years, or 6 to 12 years), duration of effusion (less than 4 weeks, 4 to 8 weeks, or more than 8 weeks), and whether or not an antimicrobial drug had been used for OM in the preceding 60 days in the D & A Trial; according to age (7 to 23 months, 2 to 5 years, or 6 to 12 years), duration of effusion (less than 4 weeks, 4 to 8 weeks, or more than 8 weeks), and whether an antimicrobial drug had been administered during the preceding two months for the OM present at entry in the AB I Trial; and according to duration of MEE (less than 4 weeks, 4 to 8 weeks, or more than 8 weeks) and laterality of MEE (unilateral or bilateral) in the AB II Trial. Subjects were then randomly assigned to treatment groups (D/A or Placebo in the D & A trial; Amoxicillin/Placebo, Amoxicillin/D/A, or Placebo/Placebo in the AB I trial; and Erythromycin-Sulfisoxazole, Cefaclor, Amoxicillin, or Placebo in the AB II trial). Antibiotic or its placebo was administered for 2 weeks; D/A or its placebo was administered for 4 weeks. All subjects were to be followed over a 4-week period, which consisted of two follow-up visits (one at the end of 2 weeks and the other at the end of 4 weeks). All medication was dispensed in a double-blind fashion and all observations at follow-up visits were made by blinded observers. The primary outcome measure in each trial was the prevalence of MEE, as determined by an algorithm combining otoscopy and tympanometry, 2 and 4 weeks after entry.

1.4 OBJECTIVES

We postulate that covariates, laterality in particular, have a strong association with outcome based upon the literature and the results of the original series of efficacy trials. Specifically, these analyses address the question whether the bilateral condition is simply a more intense case of unilateral disease or, alternatively, whether bilateral disease represents a novel condition to each ear of the individual child (Johnson, 1997). If the latter case is true, it is possible that the ears of the individual are biologically different and provide varying environments within which OME is allowed to thrive to greater or lesser degrees. To address these and other related questions, the following aims shall be addressed:

(1) a) Assess whether the prevalence of effusion is similar in right ears and left ears at each time point, and b) the extent to which prevalence in right ears and left ears is associated

with other baseline covariates such as age, duration of effusion, treatment arm and gender.

(2) a) Describe the transitions in laterality status of effusion at 2 weeks and 4 weeks, and b) assess the extent to which the transitions in effusion status are associated with other baseline covariates such as age, duration of effusion, treatment arm and gender.

(3) Assess whether the outcomes of left ears and right ears are independent by analyzing the responses of contralateral ears at each timepoint.

We expect that these analyses will demonstrate that laterality is a risk factor, confirming the findings of many previous studies. However, our question of interest, one we believe has not been asked before, is whether a bilateral ear represents a tougher disease. By "tougher disease," we mean that bilateral disease may represent an increased influence, or more complex interaction, of local factors not observed in the unilateral condition. The novel aspect of this investigation is to gain insight as to whether this occurrence relates simply to the fact that there are two ears that must be "cured" before the child is considered effusion-free or whether there are biological differences between bilaterally and unilaterally involved ears.

2.0 LITERATURE REVIEW OF STATISTICAL METHODS

2.1 CORRELATED DATA

The original studies were randomized, double-blinded, and placebo-controlled efficacy trials involving infants and children ages seven months to 12 years who had OME. The trials measured the association between treatment and outcome using odds ratios, and by comparing the proportions of subjects without effusion at each timepoint using chi square statistics. Subject characteristics that could influence outcome, such as age, race, sex, laterality, duration of effusion and season of the year, were balanced over treatment groups and were tested for their association with outcome using logistic regression. In order to investigate higher-order interactions and to control for confounders, analyses of children at 2 and 4 weeks also were conducted using logistic regression.

One shortcoming of the original trials was that both the longitudinal nature of the data and correlation between ears was not addressed in the analysis. It is reasonable to assume that the repeated measures of individual subjects are likely to be correlated and, thus, in this investigation we will account for the correlation in the data from baseline over the time points of 2 and 4 weeks. One option would be to use generalized estimating equations (GEEs) at the subject level; however, due to two levels of correlation, one between ears of the individual subject and the other between time points, the correlation matrix structure is difficult to define.

We will define a composite outcome variable and use transition matrices to describe the data, and model the transition probabilities in left and right ears in subjects with unilateral or bilateral manifestations of disease at entry.

2.2 TRANSITION MODELS

Transitional models can be used to model a discrete-time stochastic process. If there are countable states, at each time point the system may have changed states from the previous time point or the system may have stayed in the same state. The changes of state are called transitions. For example, if a state set includes (No Effusion, Unilateral Right, Unilateral Left, Bilateral or Missing), a child may be a bilateral case at baseline and change into a unilateral right case at 2 weeks. Let Y_{it} be the state of *i*th subject at time t (t = 0, 2 and 4 weeks) and $\mathbf{Y}_i = (Y_{i1}, Y_{i2}, \ldots, Y_{in})'$ be the complete observation vector of the *i*th subject. The process $\mathbf{Y_i}$ is a Markov chain if given the present state, the future and past states are independent. Formally,

$$P(Y_{i(t+1)} = y \mid Y_{it}, \ldots, Y_{i1}) = P(Y_{i(t+1)} = y \mid Y_{it})$$

A Markov chain of order *q* where *q* is finite satisfies

$$P(Y_{i(t+1)} = y \mid Y_{it}, \ldots, Y_{i1}) = P(Y_{i(t+1)} = y \mid Y_{it}, \ldots, Y_{i(t-q)})$$

Denote $\mathbf{X}_{it}$ as a vector of covariates for the ith subject at time t and $\boldsymbol{\beta}$ as the associated vector of regression coefficients. Let the set of states be $\{a_0, a_1, \ldots, a_K\}$. Define $\mathbf{H}_{it} = (Y_{i(t-1)}, Y_{i(t-2),} \ldots, Y_{i(t-q)}, X_{i(t-1)}, X_{i(t-2),} \ldots, X_{i(t-q)})$, the history of *i*th subject at visit t. The conditional transition probabilities $P(Y_{it} = a_k \mid Y_{i(t-1)}, \ldots, Y_{i(t-q)})$ are parameterized by the time series model proposed by Zeger and Qaqish (1988),

$$\log P(Y_{it} = a_k \mid \mathbf{H}_{it}) = \mathbf{X'}_{it} \beta + \sum_{l=1}^{q} \theta_l f_l(\mathbf{H}_{it}) ,$$

where f_l are functions of the past q outcomes and θ_l is the coefficient corresponding to f_l. A special case would be when $f_l(\mathbf{H}_{it}) = y_{t-l}$ and the model is the time series of order q,

$$\log P(Y_{it} = a_k \mid \mathbf{H}_{it}) = \mathbf{X'}_{it} \beta + \sum_{l=1}^{q} \theta_l y_{i(t-l)} .$$

Additionally, when q=1, this model reduces to the first-order Markov model

$$\log P(Y_{it} = a_k \mid \mathbf{H}_{it}) = \mathbf{X'}_{it} \beta + \theta \ y_{i(t-1)} .$$

Namely, the log of the probability of current state Y_{it} is a linear function of covariate $\mathbf{X}_{it}$ and the previous state $Y_{i(t-1)}$. Denote $P_{lm} = P(Y_{it} = l \mid Y_{i(t-1)} = m)$. The likelihood

$$L(\mathbf{Y}_1, \mathbf{Y_2}, \ldots, \mathbf{Y_n}) = \sum_{i=1} \left[Y_{i1} \log P_1 + \sum_{t=2} P_{lm}(t)^{I(Y_{i(t-1)}=l) I(Y_{it}=m)} \right]$$

will be maximized to obtain the estimates of the βs and θs.

2.3 MULTINOMIAL REGRESSION

Multinomial regression of a K-level outcome can be considered as simultaneously estimating (K-1) generalized binary logits for chosen comparison groups. Other comparisons can be computed from the current model. For example, with five nominal outcomes {Unilateral Right, Unilateral

Left, Bilateral, No Effusion, Missing}, if "No Effusion" is chosen as the baseline level, the model will be constructed based on

$$\log\left\{\frac{\Pr(\text{Unilateral Right}\mid x)}{\Pr(\text{No Effusion}\mid x)}\right\}=\beta_{0,\text{Unilateral Right}|\text{NoEffusion}}+\beta_{1,\text{Unilateral Right}|\text{NoEffusion}}\cdot x$$

$$\log\left\{\frac{\Pr(\text{Unilateral Left}\mid x)}{\Pr(\text{No Effusion}\mid x)}\right\}=\beta_{0,\text{Unilateral Left}|\text{NoEffusion}}+\beta_{1,\text{Unilateral Leftt}|\text{NoEffusion}}\cdot x$$

$$\log\left\{\frac{\Pr(\text{Bilateral}\mid x)}{\Pr(\text{No Effusion}\mid x)}\right\}=\beta_{0,\text{Bilateral}|\text{NoEffusion}}+\beta_{1,\text{Bilateral}|\text{NoEffusion}}\cdot x$$

$$\log\left\{\frac{\Pr(\text{Missing}\mid x)}{\Pr(\text{No Effusion}\mid x)}\right\}=\beta_{0,\text{Missing}|\text{NoEffusion}}+\beta_{1,\text{Missing}|\text{NoEffusion}}\cdot x,$$

where β_0 is the intercept and β_1 is the slope. For each equation there is a unique intercept and slope. The comparison between other levels is a linear combination of the above formula, for example

$$\log\left\{\frac{\Pr(\text{Bilateral}\mid x)}{\Pr(\text{Unilateral Right}\mid x)}\right\}=(\beta_{0,\text{Missing}|\text{NoEffusion}}-\beta_{0,\text{Unilateral Right}|\text{NoEffusion}})+(\beta_{1,\text{Missing}|\text{NoEffusion}}-\beta_{1,\text{Unilateral Right}|\text{NoEffusion}})\cdot x$$

In STATA, this model is implemented by the function mlogit.

2.4 GENERALIZED ESTIMATING EQUATIONS

The GEE approach was introduced by Liang and Zeger (Liang and Zeger, 1986). It allows regression modeling of longitudinal data by specifying only the mean and variance of the outcome variables and a "working" correlation structure. GEE is defined as the solution of the estimating equation

$$\sum_{i=1}^{n} d(\mathbf{X}_i;\boldsymbol{\beta})c(\mathbf{X}_i;\boldsymbol{\alpha})^{-1}\{\mathbf{Y}_i-\boldsymbol{\mu}_i\}=0,$$

where $\mathbf{X_i}$ is the vector of independent variables for subject *i* , $\boldsymbol{\mu_i}$=h($\mathbf{X_i}\boldsymbol{\beta}$) is the estimated mean of observation $\mathbf{Y_i}$, and h is a link function. The T×T matrix c($\mathbf{X_i}$; $\boldsymbol{\alpha}$) is the “working” parametric model for the covariance matrix var($\mathbf{Y_i}|\mathbf{X_i}$). It is chosen by the investigator. The p × T matrix d($\mathbf{X_i}$; $\boldsymbol{\beta}$) is a fixed function of $\mathbf{X_i}$ and $\boldsymbol{\beta}$ with $\mathrm{d}(\mathbf{Xi};\boldsymbol{\beta}) = \{\partial h(\mathbf{X}_i;\boldsymbol{\beta})/\partial\boldsymbol{\beta}\}$.

The important feature of GEE is that under mild regularity conditions, GEE has a solution that is consistent for estimating $\hat{\boldsymbol{\beta}}$ and asymptotically normal, regardless of the misspecification of the working correlation matrix. A robust sandwich-type estimator can be adopted to obtain a consistent estimate of the variance even when the working correlation matrix is mis-specified (Huber, 1967; White, 1982).

3.0 METHODS

3.1 DATA STRUCTURE

These data provide information on laterality at each time point as well as the effusion status of individual ears of the subject. A subject-level predictor is unilateral or bilateral status. Using the information on individual ears, the unilateral group can be split into left and right categories to assess differences in prevalence related to sidedness. A new variable, category of effusion, will be created to assess whether left ears and right ears in unilateral left, unilateral right, and bilateral ears behave differently over time.

The data are in "wide" format and will need to be converted into "long" form to assess the transition probabilities of effusion at 2 weeks and 4 weeks used to address objective 2). The first 4 records will be checked to make sure that the data were restructured correctly and all variables involved in the conversion are properly displayed. In addition to unilateral-right ears, unilateral-left ears and bilateral ears, missing observations at the ear-level and ears that become effusion-free at 2 weeks can be tracked over time. Category of effusion will be a 5-level variable. The previous category of effusion (lag1) will link present effusion status with prior effusion status from 0 to 2 weeks and 2 to 4 weeks.

To address aim 3) the data will be kept in long form. At each timepoint 2 records will be created, one for each ear. For example, subject 1 at baseline has separate records for the left and right ears. A variable denoting the effusion status of each contralateral ear also is created. Data will be sorted by subject, time point, and ear. For a record of left-ear status, contralateral ear status is defined as the status of the right ear in the same subject at a specified time. Likewise, for a record of right-ear status, contralateral ear status is defined as the status of the left ear in the same subject at a specified time.

3.2 DATA INVESTIGATION AND CODE CHECKING

Measures to ensure data security and to verify code include basic checks of whether the numbers of subjects in each trial match those used for the original analyses. Replications of a few of the findings of the original trials, particularly those related to effusion status at each time point, will provide reassurance that further analyses are based on accurate data. Counts will be tabulated to assess whether the distributions of individual variables were similar for each of the 3 original trials. Frequency tables will be created for baseline demographics and prognostic factors by study. The frequency of the outcome of subject-level effusion at each time point, by study and treatment, will be checked against the results of the original studies. Redundant variables will be removed.

Variable xoccup will be created to reduce the original 8-level parental occupation variable to only 4 levels: combining executive, small business and skilled occupations into one group; clerical and semiskilled occupations into a second group; welfare, unemployed, or other occupations into a third group; and unknown occupations into the fourth group. Treatment effects across the 3 trials will be compared to determine whether some treatments can be combined. The variable subject effusion, denoted sbjom, refers to a subject who has OME, coded as 1 when subject has effusion in at least one ear, or coded as 0 when the subject does not have effusion at all, at a specified timepoint. The laterality the disease is not indicated by the variable sbjom. The variables ome1r1, ome1l1, and so forth do not specify laterality of disease; instead, each specifies the condition of an ear at a specified timepoint. The variables to be included in this analysis are defined in Table 2.

Table 2. List of Variables

variable name	storage type	display format	variable label
durgrp	byte	%8.0g	Duration of OME at entry
season	byte	%8.0g	Season at entry
ome1r1	byte	%11.0g	OME (R ear) at entry visit
ome1l1	byte	%11.0g	OME (L ear) at entry visit
sbjom11	byte	%11.0g	OME (subject) entry visit
ome1r2	byte	%11.0g	OME (R ear) at 2 wk visit
ome1l2	byte	%11.0g	OME (L ear) at 2 wk visit
sbjom12	byte	%11.0g	OME (subject) at 2 wk visit
ome1r4	byte	%11.0g	OME (R ear) at 4 wk visit
ome1l4	byte	%11.0g	OME (L ear) at 4 wk visit
sbjom14	byte	%11.0g	OME (subject) at 4 wk visit
rtrt	byte	%11.0g	Treatment
study	byte	%8.0g	Study
gender	byte	%8.0g	Gender
xlat	byte	%10.0g	Laterality of OME at entry
xrace	byte	%8.0g	Race
xpreab	byte	%11.0g	Antimicrobials rec'd in past 8 weeks
xage	byte	%8.0g	Age at entry
xhxdx	byte	%10.0g	History of ear disease
xuri1	byte	%8.0g	Upper respiratory infection at entry
xhear	byte	%8.0g	Average hearing (SRT/SAT) at entry
id	int	%8.0g	ID
xoccup	float	%21.0g	Occupation of primary wage earner

In total, 1448 subjects from the 3 trials were included in this study. Overall, 7.25% (105 of 1448) of outcome variables were missed at the 2-week endpoint and 8.36% (121 of 1448) were missed at the 4-week endpoint. We feel this is a relatively low number of missing observations and therefore no missing data analysis is planned other than to include "missing" as a separate category in the analysis. A check of missing observations revealed that only 4 subjects at the 2 week time point and only 5 subjects at the 4 week time point had a missing observation for one ear and were treated as completely missing.

3.3 DESCRIPTIVE ANALYSIS

3.3.1 Aim 1

A table will be constructed to show prevalence of effusion at baseline, 2 weeks, and 4 weeks. Frequencies will be calculated for each laterality group as well as for subgroups of unilateral subjects who experienced either variant of unilateral disease, right-ear effusion or left-ear effusion. These descriptives will be shown overall, and separately for each treatment arm.

3.3.2 Aim 2

Transition matrices will be constructed to provide a description of the data over time. The progress of individual ears of subjects will be tracked from 0 to 2 weeks and from 2 to 4 weeks. The 3X5 transition matrix created for the baseline to 2-week time period will assign all subjects to unilateral right, unilateral left, or bilateral effusion groups at baseline, as all subjects coming into the study had some type of effusion and could not have had a missing outcome. At two weeks it was possible for subjects to experience no effusion or be missing in addition to having effusion in right or left ear only or in both ears. A 5X5 transition matrix will summarize transitions from the 2 to 4 week time points

3.3.3 Aim 3

The baseline to 2-week transition matrix will summarize the conditional probabilities of effusion at the 2-week timepoint. The 2 to 4-week matrix will summarize the corresponding conditional probabilities for the 4-week timepoint. The dependence of subjects' current effusion status on prior status can be viewed using this method; this information cannot be discerned from prevalence measures.

3.4 STATISTICAL MODELING

In preliminary analyses, we will assess whether some of the treatment arms from the 3 studies can be combined in the present analysis. Using data on the ear-level, a GEE analysis will be conducted with outcome OME and covariates including treatment and week. The working covariance structure is assumed to be exchangeable. A robust estimate of standard error will be used. Non-significant treatments will be combined with placebo. Among the treatments found to be significantly different from placebo, pair-wise comparisons will be conducted to check whether any can be grouped together.

3.4.1 Aim 1

McNemar's test will be used to assess whether there are differences in prevalence associated with unilateral-right and unilateral-left manifestations of OME at 2 weeks and 4 weeks. A 2×2 table of left versus right ear will summarized the data for the matched pairs at each timepoint.

The test focuses on discordant pairs and each ear is expected to have the same probability of OME under the null hypothesis. The null hypothesis of prevalence unilateral-right = prevalence unilateral-left, which is to say similar numbers of discordant pairs occur in both off-diagonal cells, will be rejected if $p < 0.05$. Separate tests will be conducted at 2 weeks and 4 weeks.

Multinomial regression will be used to assess baseline covariates associated with prevalence at each time point. Category of effusion will be regressed on prognostic variables and baseline demographic characteristics of interest. Selection will begin with the inclusion of all variables in the model. Those variables without a p-value of less than 0.20 will be dropped and the remaining variables will be regressed successively at the alpha = 0.10 level until only statistically significant covariates remain. Once a final model is obtained, Wald tests comparing the unilateral-left and unilateral-right ears will be conducted at the alpha = 0.05 level for each of the statistically significant covariates to assess whether prevalence differs by sidedness of OME.

3.4.2 Aim 2

The variable, category of effusion at previous time point, in addition to the other covariates of interest, will be regressed on current category of effusion using multinomial regression to assess status of effusion over time. Selection will begin with all variables found to have had a statistically significant association on prevalence at baseline, 2 weeks, or 4 weeks. Category of effusion will be regressed on covariates in the data set at the alpha = 0.20. Model selection will continue until a final model contains only variables significant at alpha = 0.10. Variables like age, if not found significant at alpha = 0.10, may be included in our final model if deemed to have biological importance. For example, we choose, a priori, to look more carefully at the variables season of entry, upper respiratory tract infection, or duration of effusion, in addition to age, as involvement of the Eustacian tube may be a confounder on laterality and MEE. Once we have identified the most statistically significant covariates, our aim is to describe associations between levels of these variables and effusion in unilaterally and bilaterally affected children.

3.4.3 Aim 3

Under an assumption of independence, the proportion of bilateral children who become effusion-free in both ears is expected to approximately equal the multiplied proportions of those who had resolution in one ear only. By separating the bilateral subjects into 3 categories (no ears resolved, unilateral, and both ears resolved) and doubling the total to account for all ears in the subsample, expected frequencies in each of the above 3 categories can be calculated by summing the number of ears experiencing effusion and dividing by total number of ears. For example, if at 2 weeks 149 subjects are effusion-free, 84 subjects have right-ear effusion, 75 subjects have left-ear effusion, and 660 subjects have bilateral effusion, the total number of ears is 1936, among which 1479 have effusion, then $P_t = 1479/1936 = .764$. If, then, the marginal probability of effusion in all ears is (P_t), then the expected probabilities of bilateral effusion, unilateral effusion, and no effusion are P_t^2, $2P_t(1-P_t)$, and $(1-P_t)^2$, respectively. A chi-squared goodness of fit test, with alpha set at 0.05, will then be conducted to assess whether the data matched what we expected under the null hypothesis of independence,

$$\sum \frac{(O-E)^2}{E} \sim \chi^2(1)$$

A rejection of this hypothesis, in a manner where fewer bilateral children than expected were effusion-free, may indicate more severe disease in bilateral ears. This process yields a time-specific measure of independence between ears at the 2-week and 4 week time points. This approach assumes no difference between the probabilities of effusion by sidedness, although it could be adapted to account for such differences.

Modeling of contralateral ears of the entire sample using GEE on the ear-level will quantify the extent of dependence one ear has relative to the effusion status of the other within each subject. The outcome is OME and covariates include sidedness, contralateral ear status, and categorical variables for time. The working covariance structure is assumed to be exchangeable. A robust estimate of standard error is used.

Table 3. Contralateral Ear Status Data Structure

id	week	ear	OME	cs
1	0	Right	Effusion	Effusion
1	0	Left	Effusion	Effusion
1	2	Right	Effusion	No Effusion
1	2	Left	No Effusion	Effusion
1	4	Right	Effusion	Effusion
1	4	Left	Effusion	Effusion
2	0	Right	Effusion	Effusion
2	0	Left	Effusion	Effusion
2	2	Right	.	.
2	2	Left	.	.
2	4	Right	.	.
2	4	Left	.	.
4	0	Right	Effusion	No Effusion
4	0	Left	No Effusion	Effusion
4	2	Right	No Effusion	Effusion
4	2	Left	Effusion	No Effusion
4	4	Right	No Effusion	No Effusion
4	4	Left	No Effusion	No Effusion

4.0 RESULTS

Table 4 shows the results of the preliminary GEE analysis of the prevalence of effusion by treatment group over time, which justified a combining of treatments. Based on efficacy of the various treatments, the 6 treatments were combined into 2 groups by combining E-S, D/A, and Placebo (coded as "0") and by combining Amoxicillin, Amoxicillin and D/A, and Cefaclor (coded as "1"). D/A and E-S were not statistically significantly different from placebo. Amoxicillin, Amoxicillin and D/A, and Cefaclor all were significant in reducing effusion. Pair-wise comparisons shown below the table show that these 3 effective treatments are not significantly different from one another.

Table 4. Estimated Log Odds of Effusion by Treatment and Time

	Log Odds	Semi-robust Std. Err.	z	P>|z|	[95% Conf. Interval]	
D/A	**-0.138**	0.108	-1.28	**0.199**	-0.350	0.073
Amoxicillin	-0.528	0.109	-4.83	0.001	-0.743	-0.314
Amoxicillin/D/A	-0.507	0.128	-3.96	0.001	-0.757	-0.256
E-S	**-0.221**	0.180	-1.23	**0.219**	-0.573	0.132
Cefaclor	-0.403	0.181	-2.22	0.026	-0.757	-0.048
Week 2	-1.066	0.056	-19.05	0.001	-1.176	-0.957
Week 4	-1.320	0.058	-22.8	0.001	-1.434	-1.207
_cons	2.027	0.076	26.77	0.001	1.879	2.176

- **Test for Amoxicillin=Amoxicillin/D&A, chi2(1) =0.02, Prob> chi2 = 0.878;**
- **Test for Amoxicillin=Cefaclor, chi2(1) = 0.44, Prob > chi2 = 0.506**

4.1 BASELINE DEMOGRAPHIC CHARACTERISTICS IN THE COMBINED STUDY POPULATION

There were 1034 bilateral subjects, 202 unilateral-right subjects, and 212 unilateral-left subjects at baseline (Table 5). Baseline characteristics were similar for unilateral-right and unilateral-left subjects. Bilateral subjects were generally similar to subjects with unilateral OME except for having relatively more subjects with longer durations of effusion and/or upper-respiratory tract infections at baseline.

Table 5. Baseline Demographics by Laterality of OME at Study Entry

%	Unilateral Right (N=202)	Unilateral Left (N=212)	Bilateral (N=1034)
Overall	14.64	13.95	71.41
Study			
D & A	44.8	39.1	42.0
AB I	36.3	39.1	34.2
AB II	18.9	21.8	23.8
Treatment			
Placebo/D&A/E-S	63.4	61.8	66.0
Amoxicillin/Amox D&A/Cefaclor	36.6	38.2	34.0
Gender			
Female	40.6	37.6	40.4
Male	59.4	62.4	59.6
Race			
White	73.1	71.3	75.1
Black	25.9	27.7	24.3
Unknown	0.9	1.0	0.6
Age at entry			
>=2yrs	69.3	66.3	70.5
< 2yrs	30.7	33.7	29.5
Occupation of primary wage earner			
Exec/Sm.bus/Skld	45.3	37.1	38.1
Clerical/Semiskld	17.0	20.3	22.5
Welfare/Unempld/Other	33.5	39.1	37.4
Unknown	4.2	3.5	1.9
Duration of OME at entry			
0-3 wks	18.4	22.8	**14.5**
4-8 wks	19.8	20.3	**14.1**
> 8 wks	33.5	25.7	**35.7**
Unknown	28.3	31.2	**35.7**
Antimicrobials received in past 8 wks			
No Ab received	28.8	32.2	38.7
Ab received	71.2	67.3	61.3
Unknown	0.0	0.5	0.0
History of ear disease			
No history	11.8	9.4	14.5
History	88.2	90.1	85.2
Unknown	0.0	0.5	0.3
Season at entry			
Winter	35.8	33.7	36.8
Spring	28.8	28.2	29.8
Summer	14.2	16.3	12.6
Fall	21.2	21.8	20.9
Upper respiratory infection at entry			
(-) URI	70.3	69.8	**61.7**
(+) URI	16.0	20.3	**27.7**
Unknown	13.7	9.9	10.6

4.2 PREVALENCE OF EFFUSION BY LATERALITY OVER TIME

Table 6 shows the prevalence of effusion at baseline, 2 weeks, and 4 weeks. Effusion is summarized on laterality defined at the subject level. Subjects who had unilateral disease in right ears and left ears at baseline were almost equally likely to have no effusion at 2 weeks, 24.3% (49 of 202) and 26.4% (56 of 212), respectively (Odds Ratio [OR] = 1.14, p = 0.56). Of 414 subjects who had unilateral effusion at baseline, 25.1% had effusion in the right ear and 22.7% had left ear effusion at 2 weeks. Right ears with effusion at baseline were slightly more likely than left ears to remain unilateral and have effusion in the same ear at the first follow-up visit, 49% (99 of 202) and 42% (89 of 212), respectively. Each group of unilateral subjects had very few instances of disease moving ear to ear, i.e. as the originally affected ear became effusion free the contralateral ear rarely developed effusion at the 2-week timepoint. These subjects (only 2.5% of 202 in those entering with unilateral effusion in the right ear alone and 2.4% of 212 in those entering with effusion exclusively in the left ear) ceased to have effusion in the originally affected ear but experienced an incident case of unilateral disease in the contralateral ear.

Table 6. Prevalence of Effusion by Timepoint and Laterality (N = 1448 subjects)

Timepoint	Baseline OME	N	No Effusion	Unilateral Right	Unilateral Left	Bilateral	Missing
Baseline	Total	1448	---	14.0	14.6	71.4	---
2 week	Bilateral	1034	14.4	8.1	7.3	63.8	6.4
	Unilateral	414	25.4	25.1	22.7	16.7	10.1
	R only	202	24.3	49.0	2.5	14.9	9.4
	L only	212	26.4	2.4	42.0	18.4	10.9
4 week	Bilateral	1034	19.1	8.3	8.8	56.1	7.7
	Unilateral	414	33.6	17.4	20.3	18.1	10.6
	R only	202	35.2	33.2	3.5	18.3	9.9
	L only	212	32.1	2.4	36.3	17.9	11.3

Subjects with unilateral disease in right ears and left ears at baseline were about equally likely to have no effusion at 4 weeks, 35.2% (71 of 202) and 32.1% (68 of 212). Of 414 subjects who had unilateral effusion at baseline, 17.4% had effusion in the right ear and 20.3% had left ear effusion at 4 weeks. At 4 weeks, unilateral effusion remained in left ears slightly more often than in right ears, 36.3% (74 of 202) and 33.2% (71 of 212), respectively. Once again, incidence of effusion in the contralateral ear is quite uncommon in those subjects whose originally affected ear had become free of effusion (2.4% of the 202 subjects with unilateral effusion in the right ear at baseline and 3.5% of the 212 subjects entering with unilateral effusion in the left ear at baseline).

McNemar tests were conducted 2 weeks and 4 weeks to confirm that there were not left-right differences between ears, which could have accounted for differing rates of effusion among unilateral effusion groups in the original trials. Among unilateral subjects, the numbers who had effusion in the right ear (104) and in the left ear (94) were not significantly different at 2 weeks, (OR = 1.106; 95% CI [0.829, 1.478]). At 4 weeks, the numbers of subjects with unilateral-right effusion (72) and unilateral-left effusion (84) were not significantly different, (OR = 0.858; 95% CI [0.617, 1.188]). These odds ratios are the ratios of unilateral left over unilateral right.

Prevalence of effusion was described by treatment arm in Table 7. McNemar tests also were carried out by treatment arm at 2 and 4 weeks. In the Placebo/D/A/E-S treatment arm, the OR = 1.25 for unilateral-left relative to unilateral-right and the 95% CI is (0.889, 1.765). The Amoxicillin/Amox. and D/A/Cefaclor arm had OR = 0.65 for unilateral-left relative to unilateral-right and the 95% CI is (0.297, 1.373). These results showed no significant difference in prevalence of effusion either between right and left ears in either treatment arm.

Table 7. Prevalence of Effusion by Timepoint, Laterality, and Treatment

a) Placebo/D/A/E-S

Timepoint	Baseline OME	N	No Effusion	Unilateral Right	Unilateral Left	Bilateral	Missing
Baseline	Total	942	---	13.6	13.9	72.5	---
2 week	Bilateral	683	10.4	6.7	7.8	68.1	7.0
	Unilateral	259	20.5	28.6	22.8	18.5	9.7
	R only	128	21.1	53.9	2.3	14.8	7.8
	L only	131	19.9	3.8	42.8	22.1	11.4
4 week	Bilateral	683	16.5	8.6	7.5	58.7	8.6
	Unilateral	259	30.9	18.9	19.7	20.5	10.0
	R only	128	32.0	37.5	1.6	20.3	8.6
	L only	131	29.8	0.8	37.4	20.6	11.5

b) Amoxicillin/Amoxicillin and D/A/Cefaclor

Timepoint	Baseline OME	N	No Effusion	Unilateral Right	Unilateral Left	Bilateral	Missing
Baseline	Total	506	---	14.6	16.0	69.4	---
2 week	Bilateral	351	22.2	10.8	6.3	55.6	5.1
	Unilateral	155	33.6	19.4	22.6	13.5	11.0
	R only	74	29.7	40.5	2.7	14.9	12.2
	L only	81	37.0	0.0	40.7	12.4	9.9
4 week	Bilateral	351	23.9	7.7	11.4	51.0	6.0
	Unilateral	155	38.1	14.8	21.3	14.2	11.6
	R only	74	40.5	25.7	6.8	14.9	12.2
	L only	81	35.8	4.9	34.6	13.6	11.1

Separate multinomial logistic models were run at baseline, 2 weeks, and 4 weeks to identify covariates associated with increased prevalence of effusion. Unilateral effusion in the right ear was the reference category for the analyses of baseline effusion (Table 8). At baseline, duration of effusion and upper-respiratory tract infection were significant predictors of category of effusion. Subjects who had upper-respiratory infection at entry had an increased relative risk (RR) compared to subjects who had unilateral-right effusion disease (RR = 1.62, p = 0.012). Likewise, subjects who had longer (>8 weeks) or unknown duration of effusion at entry were more likely to have bilateral effusion. There were no significant predictors that distinguished between left-ear and right-ear unilateral effusion at baseline (p > 0.24 for each).

Table 8. Predictors of OME at Baseline Based on Multinomial Logistic Regression Model

	Log RR	Std. Err.	z	P>|z|	[95%Conf. Interval]	
Left Effusion						
Upper-respiratory tract inf.	-0.239	0.261	-0.91	0.361	-0.750	0.273
Duration group						
4-8 weeks	0.219	0.332	0.66	0.510	-0.432	0.869
> 8 weeks	0.350	0.304	1.15	0.250	-0.246	0.945
unknown	0.135	0.299	0.45	0.652	-0.451	0.721
_cons	-0.131	0.240	-0.55	0.586	-0.601	0.340
Bilateral						
Upper-respiratory tract inf.	0.484	0.193	2.51	**0.012**	0.105	0.862
Duration						
4-8 weeks	0.066	0.262	0.25	0.801	-0.448	0.580
> 8 weeks	0.736	0.237	3.11	**0.002**	0.272	1.201
unknown	0.606	0.229	2.64	**0.008**	0.157	1.055
_cons	1.050	0.187	5.62	0.001	0.684	1.416
(cat1==R Effusion is reference outcome)						

Chi square test with df = 6	Duration of Effusion	P = 0.002
Chi square test with df = 2	Upper-respiratory tract infection	P < 0.001

The multinomial model for effusion status at 2 weeks is summarized in Table 9. "No Effusion" is the reference category for this model. The significant predictors of 2-week prevalence are treatment, male gender, occupation of primary wage-earner, upper-respiratory tract infection at baseline, and duration of effusion. The overall test statistics for these variables are summarized in the Table 9 footnote. Treatment significantly reduces the relative risk of effusion in unilateral-right, unilateral-left and bilateral groups (RR = 0.55, RR = 0.54, RR = 0.42; respectively). Subjects who had longer (>8 weeks), or unknown duration of effusion had significantly increased relative risk of having bilateral effusion at 2 weeks (RR = 2.90 and RR = 1.82, respectively).

Missing effusion status at 2 weeks was less common in male subjects and in those who received the treatment. Subjects whose primary wage-earner category was not executive/small business/skilled were more likely to be missing at 2 weeks (P = 0.045 and P = 0.001 for Clerical/Semiskilled and Welfare/Unemployed/Other groups, respectively). Duration of effusion longer than 8 weeks or unknown was much more common for subjects with missing effusion status at 2 weeks.

Table 9. Predictors of OME at 2 Weeks Based on a Multinomial Logistic Regression Model

	Log RR	Std. Err.	z	P>|z|	[95%Conf. Interval]	
Right Effusion						
Treatment Amox/Amox D&A/Cefaclor	**-0.603**	0.206	-2.92	**0.003**	-1.007	-0.199
Gender Male	-0.091	0.210	-0.44	0.662	-0.503	0.319
Occupation Clerical/semiskilled	-0.488	0.281	-1.74	0.083	-1.040	0.063
Welfare/Unemployed /other	0.218	0.231	0.94	0.346	-0.235	0.670
unknown	0.514	0.943	0.55	0.585	-1.333	2.362
Upper-respiratory tract inf.	0.029	0.232	0.13	0.899	-0.426	0.485
Duration Group 4-8 weeks	**0.673**	0.333	2.02	**0.044**	0.019	1.326
Duration > 8 weeks	**0.805**	0.303	2.66	**0.008**	0.212	1.398
unknown	0.298	0.295	1.01	0.314	-0.281	0.877
_cons	-0.420	0.314	-1.34	0.181	-1.034	0.195
Left Effusion						
Treatment Amox/Amox D&A/Cefaclor	**-0.621**	0.217	-2.87	**0.004**	-1.046	-0.197
Gender Male	-0.288	0.218	-1.32	0.186	-0.714	0.139
Occupation Clerical/semiskilled	-0.510	0.300	-1.7	0.089	-1.100	0.078
Welfare/Unemployed /other	0.271	0.241	1.12	0.261	-0.201	0.742
unknown	0.299	1.027	0.29	0.771	-1.714	2.313
Upper-respiratory tract inf.	-0.447	0.265	-1.69	0.09	-0.965	0.071
Duration Group 4-8 weeks	0.573	0.348	1.65	0.099	-0.108	1.255
Duration > 8 weeks	0.602	0.318	1.90	0.058	-0.021	1.224
unknown	0.260	0.304	0.86	0.392	-0.335	0.855
_cons	-0.273	0.320	-0.85	0.394	-0.899	0.354

Table 9 continued

	Log RR	Std. Err.	z	P>|z|	[95%Conf. Interval]	
Bilateral						
Treatment Amox/Amox D&A/Cefaclor	**-0.871**	0.158	-5.51	**0.001**	-1.181	-0.562
Gender Male	-0.083	0.162	-0.51	0.607	-0.401	0.234
Occupation Clerical/semiskilled	0.002	0.200	0.01	0.993	-0.391	0.395
Welfare/Unemployed /other	0.262	0.183	1.43	0.153	-0.097	0.621
unknown	-0.521	0.900	-0.58	0.562	-2.286	1.243
Upper-respiratory tract inf.	0.295	0.178	1.66	0.096	-0.053	0.643
Duration Group 4-8 weeks	0.326	0.263	1.24	0.216	-0.190	0.842
Duration > 8 weeks	**1.066**	0.229	4.65	**0.001**	0.616	1.515
unknown	**0.596**	0.217	2.75	**0.006**	0.171	1.022
_cons	0.671	0.239	2.81	0.005	0.202	1.139
Missing						
Treatment Amox/Amox D&A/Cefaclor	**-0.815**	0.254	-3.2	**0.001**	-1.314	-0.317
Gender Male	**-0.770**	0.248	-3.1	**0.002**	-1.257	-0.284
Occupation Clerical/semiskilled	**0.680**	0.338	2.01	**0.045**	0.016	1.343
Welfare/Unemployed /other	**1.064**	0.305	3.49	**0.001**	0.466	1.663
unknown	1.205	1.057	1.14	0.255	-0.868	3.277
Upper-respiratory tract inf.	-0.004	0.280	-0.02	0.987	-0.554	0.545
Duration Group 4-8 weeks	0.525	0.473	1.11	0.267	-0.401	1.451
Duration > 8 weeks	**1.355**	0.398	3.4	**0.001**	0.574	2.136
unknown	**0.890**	0.388	2.29	**0.022**	0.129	1.650
_cons	-1.552	0.429	-3.62	0.001	-2.393	-0.711
(cat1==No Effusion is the reference outcome)						

Chi square test with df = 4	Treatment	P < 0.001
Chi square test with df = 4	Gender	P = 0.019
Chi square test with df = 12	Occupation	P = 0.014
Chi square test with df = 4	Upper-respiratory infection	P = 0.016
Chi square test with df = 12	Duration of effusion	P < 0.001

The multinomial model for effusion status at 4 weeks is summarized in Table 10. The reference category is "No Effusion." Subjects who participated in the AB II trial had a decreased relative risk (RR = 0.53) of unilateral effusion in the right ear at 4 weeks, p = 0.052. Subjects who received Amoxicillin or Cefaclor treatment had a decreased relative risk of unilateral effusion in the right ear at 4 weeks (RR = 0.57) and a decreased relative risk of bilateral effusion at 4 weeks, p = 0.001 (RR = 0.48). Subjects with longer duration of effusion (>8 weeks) had an increased relative risk of unilateral effusion in the left ear or bilateral effusion at 4 weeks (RR = 1.95 and RR = 2.46, respectively). Subjects who had unknown duration of effusion prior to entry had an increased relative risk of bilateral effusion at the 4-week timepoint (RR = 1.58). The relative risk of bilateral effusion at 4 weeks was decreased for those who entered during the summer months (RR = 0.38).

Table 10. Predictors of OME at 4 Weeks Based on a Multinomial Logistic Regression Model

	Log RR	Std. Err.	z	P>|z|	[95%Conf. Interval]	
Right Effusion						
Study						
AB I	0.320	0.290	1.110	0.269	-0.247	0.888
AB II	**-0.634**	0.326	-1.950	**0.052**	-1.272	0.004
Treatment						
Amox/Amox D&A/Cefaclor	**-0.565**	0.280	-2.020	**0.043**	-1.114	-0.017
Gender						
Male	-0.053	0.202	-0.260	0.792	-0.450	0.343
Previous use of antibiotics	0.032	0.226	0.140	0.886	-0.411	0.475
Duration Group						
4-8 weeks	0.324	0.315	1.030	0.304	-0.294	0.942
Duration > 8 weeks	0.491	0.295	1.670	0.096	-0.087	1.069
unknown	0.104	0.301	0.350	0.729	-0.485	0.693
Season						
Spring	0.053	0.242	0.220	0.826	-0.421	0.528
Summer	-0.246	0.297	-0.830	0.408	-0.829	0.337
Fall	-0.075	0.283	-0.260	0.792	-0.629	0.480
_cons	-0.731	0.358	-2.040	0.042	-1.433	-0.028
Left Effusion						
Study						
AB I	0.368	0.288	1.280	0.202	-0.197	0.934
AB II	0.146	0.286	0.510	0.610	-0.414	0.706
Treatment						
Amox/Amox D&A/Cefaclor	-0.275	0.256	-1.070	0.283	-0.776	0.227
Gender						
Male	0.005	0.196	0.020	0.981	-0.380	0.390
Previous use of antibiotics	0.334	0.223	1.500	0.134	-0.103	0.771
Duration Group						
4-8 weeks	-0.356	0.333	-1.070	0.285	-1.009	0.297
Duration > 8 weeks	**0.670**	0.272	2.460	**0.014**	0.137	1.204
unknown	0.130	0.282	0.460	0.644	-0.423	0.683
Season						
Spring	0.022	0.235	0.090	0.927	-0.439	0.482
Summer	-0.106	0.282	-0.380	0.707	-0.658	0.447
Fall	0.040	0.275	0.150	0.885	-0.500	0.580
_cons	-1.133	0.353	-3.210	0.001	-1.825	-0.441

Table 10 continued

	Log RR	Std. Err.	z	P>|z|	[95%Conf. Interval]	
Bilateral						
Study						
AB I	**0.401**	0.211	1.900	**0.058**	-0.013	0.815
AB II	0.184	0.207	0.890	0.375	-0.222	0.590
Treatment						
Amox/Amox D&A/Cefaclor	**-0.730**	0.192	-3.810	**0.001**	-1.105	-0.354
Gender						
Male	-0.225	0.142	-1.580	0.114	-0.503	0.054
Previous use of antibiotics	-0.038	0.159	-0.240	0.812	-0.349	0.273
Duration Group						
4-8 weeks	0.093	0.232	0.400	0.689	-0.363	0.549
Duration > 8 weeks	**0.900**	0.209	4.320	**0.001**	0.491	1.309
unknown	0.456	0.206	2.210	0.027	0.052	0.861
Season						
Spring	-0.318	0.172	-1.850	0.064	-0.655	0.019
Summer	**-0.975**	0.220	-4.420	**0.001**	-1.407	-0.543
Fall	0.068	0.193	0.350	0.724	-0.310	0.446
_cons	0.670	0.250	2.680	0.007	0.180	1.160
Missing						
Study						
AB I	0.261	0.319	0.820	0.414	-0.364	0.886
AB II	-0.252	0.330	-0.760	0.445	-0.898	0.395
Treatment						
Amox/Amox D&A/Cefaclor	-0.532	0.303	-1.750	0.080	-1.126	0.063
Gender						
Male	-0.751	0.215	-3.490	0.000	-1.174	-0.329
Previous use of antibiotics	-0.444	0.238	-1.870	0.062	-0.910	0.022
Duration Group						
4-8 weeks	-0.058	0.395	-0.150	0.882	-0.833	0.716
Duration > 8 weeks	0.768	0.328	2.340	0.019	0.125	1.410
unknown	0.315	0.330	0.960	0.339	-0.331	0.961
Season						
Spring	-0.046	0.265	-0.170	0.863	-0.566	0.475
Summer	-0.292	0.321	-0.910	0.362	-0.921	0.337
Fall	-0.099	0.309	-0.320	0.749	-0.705	0.507
_cons	-0.417	0.379	-1.100	0.272	-1.160	0.326
(cat1==No Effusion is reference outcome)						

Chi square test with df = 8	Study	P = 0.057
Chi square test with df = 4	Treatment	P = 0.003
Chi square test with df = 4	Gender	P = 0.006
Chi square test with df = 4	Previous use of antibiotic	P = 0.078
Chi square test with df = 12	Duration of effusion	P = 0.001
Chi square test with df = 12	Season	P = 0.002

4.3 TRANSITION IN LATERALITY STATUS

Figure 1 shows the transition probabilities at 2 and 4 weeks for subjects with unilateral disease at baseline. To the outer extreme of the figure is baseline status of effusion and working toward the center of the figure is the conditional probability of first transition in effusion status at 2 weeks, followed by the conditional probability of effusion at the 4-week timepoint. There are 5 outcomes possible at 2-weeks upon which the 4-week effusion status is conditioned. The transitions in effusion status at 2 and 4 weeks were not possible using measures of prevalence. For example, prevalence in right ears and left ears at 2 weeks have, thus far, not reflected the particular changes in effusion status, i.e., unilateral cases that got better or worse and bilateral cases that improved.

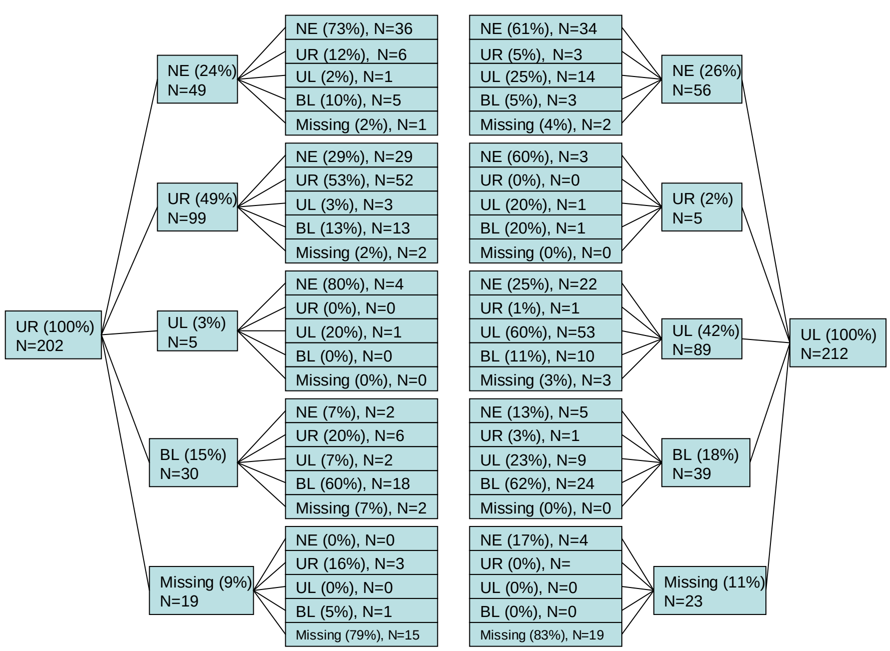

Figure 1. Transition Probabilities at 2 and 4 Weeks in Subjects with Unilateral OME at Baseline

(BL=bilateral; UR=unilateral right; UL=unilateral left)

The rates of unilateral cases becoming effusion-free from 2 to 4 weeks were similar to those from 0 to 2 weeks. Those subjects who continued to experience effusion at 2 weeks in the same ear that had been diagnosed at baseline became effusion free at the 4 week timepoint at nearly the same rate as those who had become effusion-free from baseline to the 2-week timepoint (22 of 89 [24.7%] at the 4 week timepoint in those who had left-ear effusion at baseline and 29 of 99 [29.3%] at the 4 week timepoint in those who had right-ear effusion at baseline). In accordance with the prevalence descriptives, effusion was found rarely in the contalateral ear if the originally affected ear had become free of effusion. In the few instances of effusion in the contralateral ear only at 2 weeks, the majority became effusion free at 4 weeks (4 of 5 subjects who had right-ear effusion at baseline and 3 of 5 subjects who had left-ear effusion at baseline).

There are other similar patterns in left and right ears in the 2 to 4-week transition in laterality status. The majority of unilateral ears that were effusion free at 2 weeks (49 subjects who had unilateral right OME and 56 subjects who had unilateral right OME) tend to remain effusion free at 4 weeks (73% and 61%, respectively). Those subjects who were effusion free at 2 weeks and experienced effusion again at 4 weeks were much more likely to have effusion in the ear in which effusion had been present at baseline.

Rates of subjects with unilateral involvement whose effusion status got worse were nearly the same for left and right ears at 2 weeks, 30 of 202 (14.9%) who had unilateral-right effusion at entry and 39 of 212 (18.4%) who had unilateral-left effusion at entry. These subjects were less likely to become effusion-free at 4 weeks than to remain bilateral. Additionally, for those unilateral subjects who experienced a worsening of effusion status at 2 weeks, bilateral effusion was nearly as persistent as in those who had entered the study with bilateral effusion

(Fig. 2). Overall, just over 25.4% of unilateral subjects (105 of 414) were effusion-free at 2 weeks.

Among bilateral cases (Figure 2), 15% experienced cure in only one ear, and 14% had no effusion at 2 weeks. Those subjects experiencing an "improvement" of bilateral disease (i.e. experiencing the disease localized to one ear only) included 8% with right-ear effusion and 7% with left-ear effusion. There is no evidence that left and right ears behave differently when afflicted with unilateral or bilateral disease.

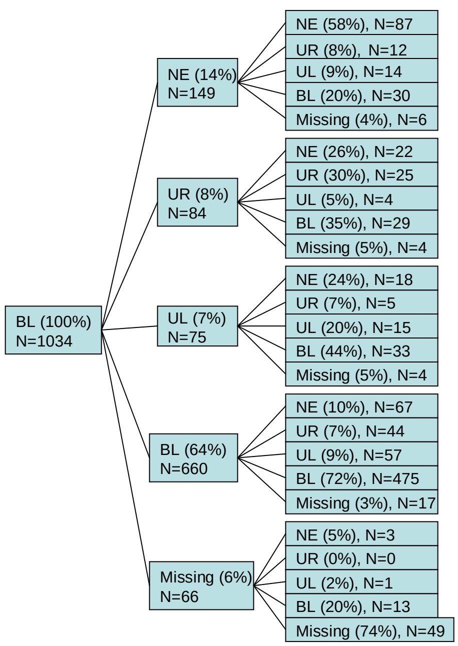

Figure 2.Transition Probabilities at 2 and 4 Weeks in Subjects with Bilateral OME at Baseline

(BL=bilateral; UR=unilateral right; UL=unilateral left)

Of the 149 subjects who were effusion-free at 2 weeks, 87 (58%) remained effusion-free at 4 weeks. Resistance to improvement at 2 weeks in those who entered with bilateral OME was not unlike that of unilateral subjects whose condition worsened at 2 weeks when observed at the 4-week timepoint. Those who entered with bilateral effusion experienced improvement at a similarly balanced rate (84 of 1034 and 75 of 1034, respectively). Of the bilateral cases who were effusion free in one ear only at the first follow-up, nearly 25% were completely effusion-free at the end of the study—roughly the same cure rate as unilateral subjects from baseline to 2 weeks.

Of the 660 subjects that had bilateral effusion at 2 weeks, 475 (72%) still had bilateral effusion at 4 weeks. Eight percent of the 660 bilateral children had their condition improve to unilateral right and 7% had their condition improve to unilateral left. Of the 149 subjects that were effusion-free at 2 weeks, 12 had right-ear effusion and 14 had left-ear effusion at 4 weeks. Thirty subjects of the 149 (20%) who had been effusion-free at 2 weeks had bilateral effusion at 4 weeks. Of the 197 subjects who were effusion-free at the study's conclusion, less than half (87) had been effusion-free at 2 weeks (22 had right ear effusion, 18 had left ear effusion, and 67 had bilateral effusion).

Modeling of the transitions was done using multinomial logistic regression. "No Effusion" is the reference category for this model. As seen in Table 11, the significant predictors of 2-week transitions of effusion status are previous effusion status, treatment, male gender, occupation of primary wage-earner, and duration of effusion. At 2 weeks, subjects who were unilateral-right at baseline were much more likely to remain unilateral-right (RR = 24.8), subjects who were bilateral at baseline were much more likely to remain bilateral (RR = 6.3), and subjects who were unilateral-left at baseline were much more likely to remain unilateral-left (RR = 1.0, compared to RR = 0.07 for unilateral-right and RR = 0.32 for bilateral; $p < 0.001$ for each). Treatment with Amoxicillin or Cefaclor reduced the RR of unilateral-right, unilateral-left, and bilateral OME at 2-weeks ($p < 0.011$ for each; RR = 0.58, RR = 0.49 and RR = 0.40, respectively). Overall, duration of effusion longer than 4 weeks prior to entry was associated with increased RR of both unilateral and bilateral effusion.

Table 11. Significant Predictors of OME for Baseline to 2 Week Transitions in Effusion Status

	Log RR	Std. Err.	z	P>|z|	[95%Conf. Interval]	
Right Effusion						
Effusion at baseline						
Unilateral-right	**3.209**	0.504	6.36	**0.001**	2.221	4.198
Bilateral effusion	**1.877**	0.490	3.83	**0.001**	0.917	2.837
Treatment						
Amox/Amox						
D&A/Cefaclor	**-0.539**	0.211	-2.55	**0.011**	-0.953	-0.125
Gender						
Male	-0.205	0.211	-0.97	0.331	-0.619	0.209
Occupation						
Clerical/semiskilled	-0.463	0.284	-1.63	0.103	-1.019	0.093
Welfare/unemployed /other	0.134	0.234	0.57	0.566	-0.325	0.594
unknown	0.936	0.745	1.26	0.209	-0.523	2.396
Duration Group						
4-8 weeks	**0.751**	0.339	2.22	**0.027**	0.087	1.416
Duration > 8 weeks	**1.065**	0.308	3.46	**0.001**	0.461	1.668
unknown	0.491	0.300	1.64	0.102	-0.097	1.079
_cons	-2.685	0.549	-4.89	0.001	-3.762	-1.608
Left Effusion						
Effusion at baseline						
Unilateral-right	**-2.733**	0.504	-5.42	**0.001**	-3.721	-1.745
Bilateral effusion	**-1.153**	0.228	-5.05	**0.001**	-1.601	-0.706
Treatment						
Amox/Amox						
D&A/Cefaclor	**-0.718**	0.217	-3.32	**0.001**	-1.143	-0.294
Gender						
Male	-0.304	0.213	-1.43	0.152	-0.721	0.112
Occupation						
Clerical/semiskilled	-0.291	0.292	-1	0.32	-0.863	0.282
Welfare/unemployed /other	0.311	0.239	1.3	0.193	-0.158	0.779
unknown	0.927	0.747	1.24	0.215	-0.537	2.391
Duration Group						
4-8 weeks	0.397	0.342	1.16	0.245	-0.272	1.067
Duration > 8 weeks	**0.524**	0.308	1.7	**0.088**	-0.079	1.127
unknown	0.330	0.297	1.11	0.266	-0.252	0.912
_cons	0.551	0.330	1.67	0.095	-0.097	1.198

Table 11 continued

	Log RR	Std. Err.	z	P>|z|	[95%Conf. Interval]	
Bilateral						
Effusion at baseline						
Unilateral-right	-0.086	0.320	-0.27	0.789	-0.712	0.541
Bilateral effusion	**1.842**	0.234	7.86	**0.001**	1.383	2.301
Treatment						
Amox/Amox						
D&A/Cefaclor	**-0.923**	0.158	-5.84	**0.001**	-1.233	-0.614
Gender						
Male	-0.035	0.160	-0.22	0.825	-0.349	0.279
Occupation						
Clerical/semiskilled	-0.026	0.201	-0.13	0.896	-0.420	0.367
Welfare/unemployed /other	0.167	0.181	0.92	0.356	-0.188	0.522
unknown	0.590	0.677	0.87	0.384	-0.738	1.918
Duration Group						
4-8 weeks	**0.477**	0.260	1.84	**0.066**	-0.032	0.985
Duration > 8 weeks	**0.983**	0.227	4.33	**0.001**	0.538	1.429
unknown	**0.501**	0.217	2.31	**0.021**	0.077	0.926
_cons	-0.579	0.301	-1.92	0.055	-1.170	0.011
Missing						
Effusion at baseline						
Unilateral-right	-0.065	0.381	-0.17	0.864	-0.811	0.681
Bilateral effusion	-0.067	0.300	-0.22	0.822	-0.656	0.521
Treatment						
Amox/Amox						
D&A/Cefaclor	-0.807	0.247	-3.27	0.001	-1.291	-0.324
Gender						
Male	-0.727	0.237	-3.06	0.002	-1.192	-0.261
Occupation						
Clerical/semiskilled	0.739	0.329	2.24	0.025	0.094	1.384
Welfare/unemployed /other	1.140	0.292	3.9	0.001	0.567	1.713
unknown	1.312	0.863	1.52	0.128	-0.379	3.004
Duration Group						
4-8 weeks	0.535	0.453	1.18	0.237	-0.352	1.423
Duration > 8 weeks	1.425	0.381	3.74	0.001	0.679	2.171
unknown	0.930	0.375	2.48	0.013	0.196	1.664
_cons	-1.617	0.456	-3.55	0.001	-2.511	-0.724
(cat1==No Effusion is the reference outcome)						

0-2 weeks

Chi Square with df = 8	Previous category of effusion	P < 0.001
Chi Square with df = 4	Treatment	P < 0.001
Chi Square with df = 4	Gender	P = 0.013
Chi Square with df = 12	Occupation	P = 0.014
Chi Square with df = 12	Duration of effusion	P = 0.003

The comparable multinomial model for the 2-week to 4-week transition is summarized in Table 12. Unilateral-right and unilateral-left subjects at 2 weeks were more likely to have effusion in the same ear at 4 weeks than in the contralateral ear, p = 0.001. Unilateral-right and unilateral-left subjects at 2 weeks had similar probabilities of bilateral effusion at 4 weeks. Bilateral subjects at 2 weeks were most likely to remain bilateral at 4 weeks (RR = 29.31). Subjects in the AB II trial had a decreased relative risk (RR = 0.41) of unilateral-right effusion at 4 weeks, p = 0.004. Males had a decreased probability of bilateral effusion at 4 weeks, p = 0.05. Subjects who entered the study in the spring or summer months had a reduced probability of bilateral effusion compared to subjects who entered during the winter, p = 0.013 and p = 0.001, respectively.

Table 12. Significant Predictors of OME for 2 to 4 Week Transitions in Effusion Status

	Log RR	Std. Err.	z	P>|z|	[95%Conf. Interval]	
Right Effusion						
Effusion at 2 weeks						
Unilateral Right	**2.369**	0.299	7.93	**0.001**	1.783	2.954
Unilateral Left	-0.005	0.498	-0.01	0.991	-0.982	0.971
Bilateral	**1.593**	0.302	5.27	**0.001**	1.000	2.186
Missing	1.071	0.733	1.46	0.144	-0.365	2.506
Study						
AB I	0.079	0.235	0.34	0.737	-0.382	0.539
AB II	**-0.901**	0.314	-2.87	**0.004**	-1.516	-0.285
Age	-0.301	0.237	-1.27	0.204	-0.766	0.163
Gender						
Male	-0.054	0.218	-0.25	0.805	-0.481	0.373
Previous use of antibiotics	0.147	0.242	0.61	0.543	-0.328	0.622
Duration Group						
4-8 weeks	0.086	0.339	0.25	0.800	-0.578	0.750
Duration > 8 weeks	0.146	0.318	0.46	0.647	-0.478	0.769
unknown	-0.148	0.325	-0.46	0.649	-0.786	0.490
Season						
Spring	0.013	0.260	0.05	0.961	-0.497	0.523
Summer	-0.219	0.317	-0.69	0.490	-0.839	0.402
Fall	-0.219	0.303	-0.72	0.470	-0.813	0.375
_cons	-1.761	0.434	-4.06	0.001	-2.611	-0.911

Table 12 continued

	Log RR	Std. Err.	z	P>|z|	[95%Conf. Interval]	
Left Effusion						
Effusion at 2 weeks						
Unilateral Right	-0.186	0.434	-0.43	0.668	-1.038	0.665
Unilateral Left	**2.262**	0.289	7.82	**0.001**	1.695	2.829
Bilateral	**1.637**	0.270	6.06	**0.001**	1.108	2.167
Missing	-0.308	1.092	-0.28	0.778	-2.448	1.833
Study						
AB I	**0.488**	0.237	2.06	**0.039**	0.024	0.953
AB II	0.235	0.265	0.89	0.376	-0.285	0.754
Age	-0.198	0.227	-0.87	0.382	-0.643	0.246
Gender						
Male	0.055	0.210	0.26	0.792	-0.356	0.467
Previous use of antibiotics	0.367	0.236	1.55	0.121	-0.097	0.830
Duration Group						
4-8 weeks	-0.575	0.357	-1.61	0.107	-1.275	0.124
Duration > 8 weeks	0.481	0.295	1.63	0.103	-0.096	1.058
unknown	-0.061	0.303	-0.2	0.840	-0.655	0.533
Season						
Spring	-0.103	0.252	-0.41	0.682	-0.597	0.390
Summer	-0.233	0.302	-0.77	0.442	-0.825	0.360
Fall	-0.094	0.292	-0.32	0.748	-0.665	0.478
_cons	-2.149	0.424	-5.07	0.001	-2.980	-1.318
Bilateral						
Effusion at 2 weeks						
Unilateral Right	**1.194**	0.279	4.28	**0.001**	0.647	1.741
Unilateral Left	**1.449**	0.288	5.04	**0.001**	0.885	2.013
Bilateral	**3.378**	0.227	14.9	**0.001**	2.934	3.822
Missing	**2.021**	0.504	4.01	**0.001**	1.033	3.009
Study						
AB I	0.282	0.187	1.5	0.132	-0.085	0.649
AB II	0.118	0.211	0.56	0.575	-0.295	0.531
Age	0.087	0.178	0.49	0.622	-0.261	0.435
Gender						
Male	**-0.324**	0.165	-1.96	**0.050**	-0.647	-0.001
Previous use of antibiotics	-0.089	0.184	-0.48	0.628	-0.449	0.271
Duration Group						
4-8 weeks	-0.101	0.273	-0.37	0.710	-0.636	0.433
Duration > 8 weeks	0.519	0.245	2.12	0.034	0.040	0.999
unknown	0.162	0.244	0.66	0.507	-0.316	0.641
Season						
Spring	**-0.497**	0.200	-2.48	**0.013**	-0.888	-0.105
Summer	**-0.990**	0.254	-3.9	**0.001**	-1.488	-0.493
Fall	-0.087	0.222	-0.39	0.695	-0.523	0.349
_cons	-1.230	0.338	-3.64	0.001	-1.891	-0.568

Table 12 continued

	Log RR	Std. Err.	z	P>|z|	[95%Conf.	Interval]
Missing						
Effusion at 2 weeks						
Unilateral Right	0.592	0.558	1.06	0.289	-0.501	1.685
Unilateral Left	0.929	0.542	1.71	0.086	-0.133	1.992
Bilateral	1.461	0.438	3.33	0.001	0.602	2.320
Missing	5.266	0.532	9.89	0.001	4.223	6.310
Study						
AB I	-0.203	0.330	-0.61	0.539	-0.849	0.443
AB II	-0.305	0.395	-0.77	0.441	-1.080	0.470
Age	0.295	0.308	0.96	0.338	-0.309	0.899
Gender						
Male	-0.615	0.287	-2.14	0.032	-1.178	-0.053
Previous use of antibiotics	-0.666	0.327	-2.04	0.042	-1.307	-0.025
Duration Group						
4-8 weeks	-0.308	0.511	-0.6	0.547	-1.309	0.694
Duration > 8 weeks	0.132	0.438	0.3	0.763	-0.727	0.991
unknown	-0.203	0.443	-0.46	0.647	-1.071	0.665
Season						
Spring	-0.240	0.358	-0.67	0.503	-0.942	0.462
Summer	-0.311	0.435	-0.72	0.474	-1.164	0.541
Fall	-0.113	0.401	-0.28	0.777	-0.898	0.672
_cons	-1.817	0.584	-3.11	0.002	-2.962	-0.672
(cat1==No Effusion is reference outcome)						

2-4 weeks

Chi square test with df = 16	Previous category of effusion	P < 0.001
Chi square test with df = 8	Study	P = 0.018
Chi square test with df = 4	Gender	P = 0.061
Chi square test with df = 4	Previous use of antibiotic	P = 0.043
Chi square test with df = 12	Season	P = 0.018

4.4 CONTRALATERAL EAR

Table 13 summarizes the observed and expected numbers of subjects who experienced each of the 3 possible outcomes (neither ear clear, unilateral effusion, or both ears clear) at 2 and 4 weeks. The expected counts are derived under the assumption that effusion resolves independently in each ear. Subjects who had one ear or both missing were excluded. The Chi

Square Goodness-of-Fit test used to test our null hypothesis of statistical independence of left and right ears at each timepoint. We reject the null hypothesis of statistical independence at both 2 and 4 weeks in (a) bilateral subjects and (b) all subjects, p < 0.001 for both.

Table 13. Observed Versus Expected Counts of Bilateral Subjects Experiencing 1 of 3 Possible Outcomes at Timepoint

a) Bilateral subjects only

	2 weeks			4 weeks		
	Expected Probability	Expected Number of Subjects	Observed Number of Subjects	Expected Probability	Expected Number of Subjects	Observed Number of Subjects
Neither ear clear	0.584	565	660	0.491	468	580
Unilateral	0.361	349	159	0.210	200	177
Both ears clear	0.056	54	149	0.090	85	197

2-Week
ChiSquare = 287.2
P < 0.0001

4-Week
ChiSquare = 174.7
P < 0.0001

b) All subjects

	2 weeks			4 weeks		
	Expected probability	Expected subjects	Observed Number of subjects	Expected probability	Expected subjects	Observed Number of subjects
Neither ear clear	0.393	526	729	0.385	510	655
Unilateral	0.468	627	357	0.236	312	333
Both ears clear	0.139	187	254	0.144	191	336

2-Week
ChiSquare = 218.6
P < 0.0001

4-Week
ChiSquare = 153.6
P < 0.0001

Table 14 summarizes the GEE modeling of the prevalence of effusion in each ear at 2 and 4 weeks, using the concurrent effusion status of the other ear as a predictor. Effusion status of a contralateral ear is a significant predictor of effusion in the other ear (OR = 1.44, $p < 0.001$). There is no significant effect of sidedness ($p = 0.86$). Overall, the prevalence of effusion is decreasing over time, OR = .37 for 2 weeks and OR = .29 at 4 weeks, compared to baseline. The estimated intraclass correlation coefficient is $\alpha = 0.19$.

Table 14. GEE Model for Contralateral Ear

Predictor	Log Odds	Semi-robust Std. Err.	z	P>|z|	[95% Conf.	Interval]
Status of contralateral ear	0.367	0.097	3.78	0.001	0.177	0.558
2 week	-1.002	0.046	-21.59	0.001	-1.093	-0.911
4 week	-1.238	0.047	-26.09	0.001	-1.331	-1.145
Ear Left vs. Right	0.011	0.063	0.18	0.860	-0.112	0.134
_cons	1.501	0.117	12.87	0.001	1.273	1.730

In summary, we have no evidence that prevalence of MEE differs by sidedness of disease at any timepoint. Our investigation of baseline covariates revealed that longer duration of effusion is associated with increased risk of bilateral effusion rather than unilateral effusion. Laterality is an important prognostic factor.

Transitions in effusion status provided information about the within subject changes over time. There was no evidence that transition status of subjects were significantly different based on the sidedness of disease. Baseline covariates were similarly associated with effusion both left and right ears. The previous state of disease has a strong association to the present state of disease. Bilateral OME takes longer to resolve than unilateral OME. At 2 weeks, the rate of no effusion in subjects who had had unilateral OME at baseline was nearly double that of subjects who had entered with bilateral OME (25.4% compared to 14.0%, respectively). Similarly, at 4 weeks, subjects who had entered the study with unilateral OME and continued to experience unilateral effusion at 2 weeks were substantially more likely to have no effusion 4 weeks than subjects who had entered with bilateral disease and continued to experience effusion at 2 weeks (29.3% compared to 10.0%, respectively).

The descriptive analysis also offered an indication of the level of dependence between the ears of each subject. A test of independence was rejected and it was concluded that the outcomes of the two ears are highly dependent. Finally, a GEE model at the ear level revealed that the effusion status of one ear is dependent on the status of the contalateral ear, with an OR of effusion of 1.44 when the contralateral ear has effusion at the same timepoint).

5.0 DISCUSSION

This investigation looked at 3 separate but related clinical trials in aggregate. The D&A trial compared the efficacy of a standard treatment (D/A) to placebo and found no evidence that treatment was effective. The ABI trial was similar to the D&A trial in design but compared an antibiotic (amoxicillin) with and without D/A to placebo and found that the antibiotic was effective at least in the short term in treating OME; D/A had no effect. The ABII compared the efficacy of 2 promising antibiotics to amoxicillin but found no evidence that either was better at treating OME than amoxicillin. We aggregated the various treatments used in these trials into two groups, based upon the effect each had on the outcome of OME. We designated the group of effective medications (amoxicillin, amoxicillin/D/A, and cefaclor) as the treatment and the remaining medications (D/A, E-S, and placebo) as the baseline group.

Our focus on left-right differences associated with prognosis was novel and this analysis has provided considerably more evidence that the bilateral ear represents a much tougher condition than unilateral disease in either ear. We found no evidence that sidedness is a statistically significant prognostic factor in children with OME at any timepoint of the study, either overall or within treatment groups. A high level of dependence between ears was first indicated by the transitions in effusion status. Current effusion status in unilateral subjects is highly dependent upon the effusion status of the originally affected ear. Generally, unilateral disease does not pass from ear to ear without an overall worsening of the subject's condition i.e., the subject begins to experience bilateral effusion. In bilateral subjects, improvement to unilateral effusion occurred at similar rates in right and left ears at each timepoint.

The multinomial regression equations provided a way to quantify the role of covariates in unilateral or bilateral expressions of disease. Upper-respiratory tract infection was found to have a pronounced association with bilateral status of effusion at baseline. Duration of effusion prior to entry seems to have been one of the most important covariates on prognosis; however, assignment of subjects to each duration category in the original trials was highly subjective. One would expect that, if OME had a standard course over time, disease would become less severe during the 4-week study; however, subjects who entered with longer duration were more likely to continue experiencing effusion or, in the case of subjects who entered with unilateral effusion, may experience a worsening of their condition. Longer duration of effusion upon entry is associated with increased relative risk of bilateral effusion compared to unilateral disease.

Prevalence offers a cross-sectional description of the data at each timepoint, but it is difficult to assess the behavior of disease over time. Transitional models offer a within subject description of disease. Effusion status of the individual subject is tracked over time and prior status is linked to current effusion status. Transitions allow one to assess the factors related to disease development and resolution. Transitions are better at identifying when a treatment effect took place. In our study, treatment was included in the 4-week prevalence model to account for possibly delayed benefits of medications that were administered for only 2 weeks.

This study detected that certain antibiotics are effective in treating OME, in contrast to many other that have concluded that antibiotics are not effective. Moreover, this study detected a beneficial effect associated with Cefaclor, which is not a finding of the original AB II trial. Our reanalysis reaffirms the importance of variables like laterality and duration of effusion on prognosis. Our reanalysis using correlated data methods augments the initial findings by further examining sidedness and documenting transitions over time.

A possible limitation of this investigation is that it was a secondary data analysis on an existing dataset. The original trials were not intended to address our specific questions. The first study had a significant number of missing observations in upper-respiratory tract infection status at entry. Because URI proved to be an important baseline covariate, those missing subjects may be important. There may be measurement error in the ascertainment of effusion status, as a subjective criterion (otoscopy) was used as part of the determination of outcome. For example, those subjects found to be effusion-free at 2 weeks and later began experiencing effusion in the ear initially involved may have been due to misclassification, i.e., effusion was present but escaped detection at 2 weeks. Finally, treatments that were not effective were combined with the placebo groups; however, the placebo groups of the 3 original trials were found to be dissimilar.

In conclusion, this investigation has reaffirmed the importance of certain antibiotic treatments and baseline covariates, like laterality and duration of effusion. We used McNemar's test to address aim 1) and found no evidence that left and right ears differ with respect to prevalence rates at 2 or 4 weeks (OR = 1.106 and OR = 0.858, respectively). Similarly, non-significant odds ratios were found when we accounted for treatment arms. For aim 2), transition matrices suggested that OME is a continuous disease process dependent on the subject's previous state. Transitions in outcome of effusion in left and right ears at each timepoint seemed relatively similar in unilateral and bilateral groups. Multinomial regression was used for each of the first 2 objectives to assess baseline covariates associated with prevalence and transitions of effusion status at each time point. We identified statistically significant prognostic factors of OME, including duration of effusion. After model selection, the tests conducted failed to show any discrepancies in prevalence of OME or in transitions of effusion status attributable to differences in left and right ears. Finally, to address aim 3), we conducted a Chi Square Goodness-Of-Fit test for the data at each timepoint and rejected our stated hypothesis of independence, $p < 0.001$. An ear-level GEE quantified the extent of dependence one ear has relative to the effusion status of the other within each subject. Effusion status of a contralateral ear was found to be a significant predictor of effusion in the other ear (OR = 1.44, $p < 0.001$). There was no significant effect of sidedness ($p = 0.86$) and bilateral disease does not resolve at the rate predicted by unilateral resolution.

APPENDIX A

DATA STRUCTURE

```
 insheet using "G:\ab4.csv", comma

(38 vars, 1448 obs)

.   g xoccup=occup

.   replace xoccup=1 if occup==2 | occup==3
(389 real changes made)
.   replace xoccup=2 if occup==4 | occup==5
(310 real changes made)
.   replace xoccup=3 if occup==6 | occup==7 | occup==8
(537 real changes made)
.   replace xoccup=9 if occup==0
(35 real changes made)
.   label variable study   "Study"
.   label variable rtrt  "Treatment"
.   label variable gender  "Gender"
.   label variable xrace   "Race"
.   label variable xage   "Age @ entry"
.   label variable durgrp  "Duration of OME @ entry"
.   label variable xpreab "Antimicrobials rec'd in past 8 wks"
.   label variable xhxdx   "History of ear disease"
.   label variable season  "Season @ entry"
.   label variable xuri1   "Upper respiratory infection @ entry"
.   label variable xoccup   "Occupation of primary wage earner"
.   label variable xlat    "Laterality of OME at entry"
.   label variable sbjom11 "OME at entry visit"
.   label variable sbjom12 "OME (subject) at 2 wk visit"
.   label variable sbjom14 "OME (subject) at 4 wk visit"
.   label variable ome1r1  "OME (R ear) at entry visit"
.   label variable ome1l1  "OME (L ear) at entry visit"
.   label variable ome1r2  "OME (R ear) at 2 wk visit"
.   label variable ome1l2  "OME (L ear) at 2 wk visit"
.   label variable ome1r4  "OME (R ear) at 4 wk visit"
.   label variable ome1l4  "OME (L ear) at 4 wk visit"
.   label variable xhear   "Avg hearing (SRT/SAT) @ entry"
.   label variable id      "ID"
```

```
.   label define wssffm   1 "Winter"2 "Spring" 3 "Summer" 4 "Fall"
.     label  define  occfm      1  "Exec/Sm.bus/Skld"  2  "Clerical/Semiskld"  3
"Welfare/Unempld/Other" ///
>   0 "Unknown" 9 "Unknown"
.     drop preab xagegrp race hxdx xlater uri1 srtr1 srtl1 sat1 rsat1 rsrtr1
rsrtl1 ///
>        avgsrt1 hear1 attrib_all_la~e occup
.   replace rtrt=0 if rtrt==2\
(552 real changes made)
.   label define studyfm  1 "D & A" 2 "AB  I" 3 "AB II"
.   label define meefm    1 "Effusion " 0 "No Effusion"
.   label define aomfm    1 "AOM" 0 "No AOM"
.   label define agefm    1 "< 2yrs" 0 ">=2yrs"
.   label define dur2fm   1 "0-3 wks" 2 "4-8 wks" 3 "> 8 wks" 4 "Unknown"
.   label define sexfm    1 "Male" 0 "Female"
.   label define latfm    1 "Bilateral" 0 "Unilateral" 9 "Unknown"
.   label define racefm   1 "Black" 0 "White"
.   label define hxdxfm   1 "History" 0 "No history"
.   label define preabfm  1 "Ab rec'd"  0 "No Ab rec'd"
.   label define urifm    1 "(+) URI"    0 "(-) URI "
.    label  define  rtrtfm    0  "Placebo"  1  "Amoxicillin"  3  "Amox/D&A"  4  "D&A"
///
>                                 7 "E-S" 8 "Cefaclor"
.   label define hrfm     1 "GE 25db" 0 "LT 25db" 9 "Unknown"
.   label values sbjom11 meefm
.   label values sbjom12 meefm
.   label values sbjom14 meefm
.   label values ome1r1 meefm
.   label values ome1r2 meefm
.   label values ome1r4 meefm
.   label values ome1l1 meefm
.   label values ome1l2 meefm
.   label values ome1l4 meefm
.   label values gender sexfm
.   label values xrace racefm
.   label values xage agefm
.   label values season wssffm
.   label values xpreab preabfm
.   label values xoccup occfm
.   label values study studyfm
.   label values xhxdx hxdxfm
.   label values xuri1 urifm
.   label values xlat latfm
.   label values xhear hrfm
.   label values durgrp dur2fm
.   label values rtrt rtrtfm
. describe
Contains data
  obs:         1,448
 vars:            23
 size:        44,888 (95.7% of memory free)
-----------------------------------------------------------------------------
--
              storage  display     value
variable name   type   format      label      variable label
-----------------------------------------------------------------------------
--
```

```
durgrp          byte   %8.0g       dur2fm     Duration of OME @ entry
season          byte   %8.0g       wssffm     Season @ entry
ome1r1          byte   %11.0g      meefm      OME (R ear) at entry visit
ome1l1          byte   %11.0g      meefm      OME (L ear) at entry visit
sbjom11         byte   %11.0g      meefm      OME at entry visit
ome1r2          byte   %11.0g      meefm      OME (R ear) at 2 wk visit
ome1l2          byte   %11.0g      meefm      OME (L ear) at 2 wk visit
sbjom12         byte   %11.0g      meefm      OME (subject) at 2 wk visit
ome1r4          byte   %11.0g      meefm      OME (R ear) at 4 wk visit
ome1l4          byte   %11.0g      meefm      OME (L ear) at 4 wk visit
sbjom14         byte   %11.0g      meefm      OME (subject) at 4 wk visit
rtrt            byte   %11.0g      rtrtfm     Treatment
study           byte   %8.0g       studyfm    Study
gender          byte   %8.0g       sexfm      Gender
xlat            byte   %10.0g      latfm      Laterality of OME at entry
xrace           byte   %8.0g       racefm     Race
xpreab          byte   %11.0g      preabfm    Antimicrobials rec'd in past 8
                                                wks
xage            byte   %8.0g       agefm      Age @ entry
xhxdx           byte   %10.0g      hxdxfm     History of ear disease
xuri1           byte   %8.0g       urifm      Upper respiratory infection @
                                                entry
xhear           byte   %8.0g       hrfm       Avg hearing (SRT/SAT) @ entry
id              int    %8.0g                  ID
xoccup          float  %21.0g      occfm      Occupation of primary wage
                                                earner
-----------------------------------------------------------------------------
--
Sorted by:
     Note:  dataset has changed since last saved
. reshape long ome1r ome1l sbjom1, i(id) j(week)
(note: j = 1 2 4)

Data                               wide   ->   long
-----------------------------------------------------------------------------
Number of obs.                     1448   ->    4344
Number of variables                  25   ->      20
j variable (3 values)                     ->   week
xij variables:
                   ome1r1 ome1r2 ome1r4   ->   ome1r
                   ome1l1 ome1l2 ome1l4   ->   ome1l
                sbjom11 sbjom12 sbjom14   ->   sbjom1
-----------------------------------------------------------------------------
. replace week=0 if week==1
(1448 real changes made)
. label variable ome1r "OME (R ear)"
. label variable ome1l "OME (L ear)"
. label variable sbjom1 "OME"
. label variable week "Week"
. g cat1=0
. replace cat1=1 if (ome1r==1 & ome1l==0)
(548 real changes made)
. replace cat1=2 if (ome1r==0 & ome1l==1)
(556 real changes made)
. replace cat1=3 if (ome1r==1 & ome1l==1)
(2418 real changes made)
. replace cat1=4 if (ome1r==. | ome1l==.)
```

```
(232 real changes made)
. g cat1p=cat1[_n-1] if week !=0
(1448 missing values generated)
. g cat1p2=cat1[_n-2] if week==4
(2896 missing values generated)
. g cat1l=cat1[_n+1] if week<4
(1448 missing values generated)
. label variable cat1 "OME at subject level"
.  label  define  catlab2  0  "No  Effusion"  1  "R  Effusion"  2  "L  Effusion"
3"Bilateral" 4 "Missing"
. label values cat1 catlab2
. label values cat1p catlab2
. label values cat1p2 catlab2
. label variable cat1p "Lag1"
. label variable cat1p2 "Lag2"
. label variable cat1l "Lead 1"
. describe
Contains data
  obs:         4,344
 vars:            24
 size:       217,200 (79.3% of memory free)
----------------------------------------------------------------------------
--
              storage  display     value
variable name   type   format      label      variable label
----------------------------------------------------------------------------
--
id              int    %8.0g                  ID
week            byte   %9.0g                  Week
durgrp          byte   %8.0g       dur2fm     Duration of OME @ entry
season          byte   %8.0g       wssffm     Season @ entry
ome1r           byte   %11.0g      meefm      OME (R ear)
ome1l           byte   %11.0g      meefm      OME (L ear)
sbjom1          byte   %11.0g      meefm      OME
rtrt            byte   %11.0g      rtrtfm     Treatment
study           byte   %8.0g       studyfm    Study
gender          byte   %8.0g       sexfm      Gender
xlat            byte   %10.0g      latfm      Laterality of OME at entry
xrace           byte   %8.0g       racefm     Race
xpreab          byte   %11.0g      preabfm    Antimicrobials rec'd in past 8
                                                wks
xage            byte   %8.0g       agefm      Age @ entry
xhxdx           byte   %10.0g      hxdxfm     History of ear disease
xuri1           byte   %8.0g       urifm      Upper respiratory infection @
                                                entry
xhear           byte   %8.0g       hrfm       Avg hearing (SRT/SAT) @ entry
xoccup          float  %21.0g      occfm      Occupation of primary wage
                                                earner
trt             float  %24.0g      trt2fm     Treatment
xlat2           float  %12.0g      xlatfm2
cat1            float  %11.0g      catlab2    OME at subject level
cat1p           float  %11.0g      catlab2    Lag1
cat1p2          float  %11.0g      catlab2    Lag2
cat1l           float  %9.0g                  Lead 1
----------------------------------------------------------------------------
--
Sorted by:  id
```

```
     Note:  dataset has changed since last saved
. g ome1e1=ome1r
(227 missing values generated)

. g ome1e2=ome1l
(228 missing values generated)

. save “G:\ab4”, replace
. reshape long ome1e, i(id week) j(ear)
(note: j = 1 2)

Data                               wide   ->   long
-----------------------------------------------------------------------------
Number of obs.                     4344   ->    8688
Number of variables                  26   ->      26
j variable (2 values)                     ->   ear
xij variables:
                          ome1e1 ome1e2   ->   ome1e
-----------------------------------------------------------------------------
. list id week ome1e ear ome1r ome1l in 1/12
. label variable ome1e "OME of ear"
. label variable ear "Ear"
. label define earlab 1 "Right" 2 "Left"
. label value ome1e meefm
. label value ear earlab

. * Confirm treatment
. iis id

. tis week

.
. xi:xtgee ome1e i.rtrt i.week, family(binomial) corr(exch) robust
i.rtrt            _Irtrt_0-8          (naturally coded; _Irtrt_0 omitted)
i.week            _Iweek_0-4          (naturally coded; _Iweek_0 omitted)

Iteration 1: tolerance = .04508525
Iteration 2: tolerance = .00035624
Iteration 3: tolerance = .00002386
Iteration 4: tolerance = 5.003e-07

GEE population-averaged model                   Number of obs      =      8233
Group variable:                         id      Number of groups  =      1448
Link:                                logit      Obs per group: min          2
Family:                           binomial                     avg=       5.7
Correlation:                  exchangeable                     max          6
                                                Wald chi2(7)      =    560.15
Scale parameter:                         1      Prob > chi2       =    0.0000

                                  Std. Err. adjusted for clustering on id)
-----------------------------------------------------------------------------
             |             Semi-robust
       ome1e |      Coef.   Std. Err.      z    P>|z|    [95% Conf. Interval]
-------------+---------------------------------------------------------------
    _Irtrt_1 |   -.528186   .1093753    -4.83   0.000   -.7425576   -.3138143
    _Irtrt_3 |  -.5068431    .127868    -3.96   0.000   -.7574598   -.2562264
    _Irtrt_4 |  -.1383911   .1077881    -1.28   0.199   -.3496518    .0728696
```

```
    _Irtrt_7 |    -.22091   .1798446    -1.23   0.219   -.5733989    .1315789
    _Irtrt_8 |  -.4025645   .1809581    -2.22   0.026    .7572358   -.0478932
    _Iweek_2 |  -1.066218   .0559656   -19.05   0.000   -1.175909   -.9565273
    _Iweek_4 |  -1.320223    .057906   -22.80   0.000    1.433717    -1.20673
       _cons |   2.027485   .0757413    26.77   0.000    1.879035    2.175935
------------------------------------------------------------------------------

. test _Irtrt_1=_Irtrt_3

 ( 1)  _Irtrt_1 - _Irtrt_3 = 0

           chi2(  1) =    0.02
         Prob > chi2 =    0.8775

. test _Irtrt_8=_Irtrt_1

 ( 1) - _Irtrt_1 + _Irtrt_8 = 0

           chi2(  1) =    0.44
         Prob > chi2 =    0.5055

. g trt=rtrt

. replace trt=1 if rtrt==3
(1044 real changes made)

. replace trt=1 if rtrt==8
(498 real changes made)

. replace trt=0 if rtrt==4 | rtrt==7
(2340 real changes made)

.
. label variable trt "combined treatment"

.  label  define  trtlab  0  "placebo/D&A/E-S"  1  "amoxicillin/amoxicillin  and
D&A/Cefaclor"
. label value trt trtlab
. save "G:\ab4treatment", replace
file G:\ab4treatment.dta saved
```

APPENDIX B

CODE FOR DISCRIPTIVE ANALYSIS AND MODELING

B.1 DESCRIPTIVE ANALYSIS

```
. use “G:\ab4”
. g trt=rtrt
. replace trt=1 if rtrt==3
(1044 real changes made)
. replace trt=1 if rtrt==8
(498 real changes made)
. replace trt=0 if rtrt==4 | rtrt==7
(2340 real changes made)
. label variable trt "combined treatment"

.  label  define  trtlab  0  "placebo/D&A/E-S"  1  "amoxicillin/amoxicillin  and
D&A/Cefaclor"
. label value trt trtlab
. iis id
. tis week
. *Prevalence table
. tab cat1 if week==0

     OME at |
    subject |
      level |      Freq.     Percent        Cum.
------------+-----------------------------------
 R Effusion |        202       13.95       13.95
 L Effusion |        212       14.64       28.59
  Bilateral |      1,034       71.41      100.00
------------+-----------------------------------
      Total |      1,448      100.00

. sort xlat xlat2
. by xlat: tab week cat1, row
-----------------------------------------------------------------------------
-> xlat = Unilateral
```

```
+-----------------+
| Key             |
|-----------------|
|   frequency     |
| row percentage  |
+-----------------+

           |                   OME at subject level
      Week | No Effusi  R Effusio  L Effusio  Bilateral   Missing |     Total
-----------+-------------------------------------------------------+----------
         0 |         0        202        212          0         0 |       414
           |      0.00      48.79      51.21       0.00      0.00 |    100.00
-----------+-------------------------------------------------------+----------
         2 |       105        104         94         69        42 |       414
           |     25.36      25.12      22.71      16.67     10.14 |    100.00
-----------+-------------------------------------------------------+----------
         4 |       139         72         84         75        44 |       414
           |     33.57      17.39      20.29      18.12     10.63 |    100.00
-----------+-------------------------------------------------------+----------
     Total |       244        378        390        144        86 |     1,242
           |     19.65      30.43      31.40      11.59      6.92 |    100.00
------------------------------------------------------------------------------
-----> xlat = Bilateral

+-----------------+
| Key             |
|-----------------|
|   frequency     |
| row percentage  |
+-----------------+

           |                   OME at subject level
      Week | No Effusi  R Effusio  L Effusio  Bilateral   Missing |     Total
-----------+-------------------------------------------------------+----------
         0 |         0          0          0      1,034         0 |     1,034
           |      0.00       0.00       0.00     100.00      0.00 |    100.00
-----------+-------------------------------------------------------+----------
         2 |       149         84         75        660        66 |     1,034
           |     14.41       8.12       7.25      63.83      6.38 |    100.00
-----------+-------------------------------------------------------+----------
         4 |       197         86         91        580        80 |     1,034
           |     19.05       8.32       8.80      56.09      7.74 |    100.00
-----------+-------------------------------------------------------+----------
     Total |       346        170        166      2,274       146 |     3,102
           |     11.15       5.48       5.35      73.31      4.71 |    100.00

. sort xlat2
. by xlat2: tab week cat1 if xlat==0, row
------------------------------------------------------------------------------
-> xlat2 = Unilateral R

+-----------------+
| Key             |
|-----------------|
|   frequency     |
| row percentage  |
```

```
+----------------+

           |                   OME at subject level
      Week | No Effusi  R Effusio  L Effusio  Bilateral   Missing |     Total
-----------+-------------------------------------------------------+----------
         0 |         0        202          0          0         0 |       202 
           |      0.00     100.00       0.00       0.00      0.00 |    100.00 
-----------+-------------------------------------------------------+----------
         2 |        49         99          5         30        19 |       202 
           |     24.26      49.01       2.48      14.85      9.41 |    100.00 
-----------+-------------------------------------------------------+----------
         4 |        71         67          7         37        20 |       202 
           |     35.15      33.17       3.47      18.32      9.90 |    100.00 
-----------+-------------------------------------------------------+----------
     Total |       120        368         12         67        39 |       606 
           |     19.80      60.73       1.98      11.06      6.44 |    100.00 


-----------------------------------------------------------------------------
-> xlat2 = Unilateral L

+----------------+
| Key            |
|----------------|
|   frequency    |
| row percentage |
+----------------+

           |                   OME at subject level
      Week | No Effusi  R Effusio  L Effusio  Bilateral    Missing |    Total
-----------+--------------------------------------------------------+---------
         0 |         0          0        212          0          0 |     212 
           |      0.00       0.00     100.00       0.00       0.00 |  100.00 
-----------+--------------------------------------------------------+---------
         2 |        56          5         89         39         23 |     212 
           |     26.42       2.36      41.98      18.40      10.85 |  100.00 
-----------+--------------------------------------------------------+---------
         4 |        68          5         77         38         24 |     212 
           |     32.08       2.36      36.32      17.92      11.32 |  100.00 
-----------+--------------------------------------------------------+---------
     Total |       124         10        378         77         47 |     636 
           |     19.50       1.57      59.43      12.11       7.39 |  100.00 
-----------------------------------------------------------------------------
-> xlat2 = Bilateral
no observations

. sort trt xlat

. by trt: tab cat1 if week==0

-----------------------------------------------------------------------------
-----
-> trt = placebo/D&A/E-S

     OME at |
    subject |
      level |      Freq.     Percent        Cum.
```

```
------------+-----------------------------------
 R Effusion |        128       13.59       13.59
 L Effusion |        131       13.91       27.49
  Bilateral |        683       72.51      100.00
------------+-----------------------------------
      Total |        942      100.00

-------------------------------------------------------------------------------
-----
-> trt = amoxicillin/amoxicillin and D&A/Cefaclor

     OME at |
    subject |
      level |      Freq.     Percent        Cum.
------------+-----------------------------------
 R Effusion |         74       14.62       14.62
 L Effusion |         81       16.01       30.63
  Bilateral |        351       69.37      100.00
------------+-----------------------------------
      Total |        506      100.00


. by trt xlat: tab week cat1, row

-------------------------------------------------------------------------------
------> trt = placebo/D&A/E-S, xlat = Unilateral

+----------------+
| Key            |
|----------------|
|   frequency    |
| row percentage |
+----------------+

           |                   OME at subject level
      Week | No Effusi  R Effusio  L Effusio  Bilateral    Missing |     Total
-----------+-------------------------------------------------------+----------
         0 |         0        128        131          0          0 |       259
           |      0.00      49.42      50.58       0.00       0.00 |    100.00
-----------+-------------------------------------------------------+----------
         2 |        53         74         59         48         25 |       259
           |     20.46      28.57      22.78      18.53       9.65 |    100.00
-----------+-------------------------------------------------------+----------
         4 |        80         49         51         53         26 |       259
           |     30.89      18.92      19.69      20.46      10.04 |    100.00
-----------+-------------------------------------------------------+----------
     Total |       133        251        241        101         51 |       777
           |     17.12      32.30      31.02      13.00       6.56 |    100.00

-------------------------------------------------------------------------------
------> trt = placebo/D&A/E-S, xlat = Bilateral

+----------------+
| Key            |
|----------------|
|   frequency    |
| row percentage |
```

```
+----------------+

           |                    OME at subject level
      Week | No Effusi  R Effusio  L Effusio  Bilateral    Missing |     Total
-----------+-------------------------------------------------------+----------
         0 |         0          0          0        683          0 |       683 
           |      0.00       0.00       0.00     100.00       0.00 |    100.00 
-----------+-------------------------------------------------------+----------
         2 |        71         46         53        465         48 |       683 
           |     10.40       6.73       7.76      68.08       7.03 |    100.00 
-----------+-------------------------------------------------------+----------
         4 |       113         59         51        401         59 |       683 
           |     16.54       8.64       7.47      58.71      8.64  |    100.00 
-----------+-------------------------------------------------------+----------
     Total |       184        105        104      1,549        107 |     2,049 
           |      8.98       5.12       5.08      75.60       5.22 |    100.00 

-----------------------------------------------------------------------------
------> trt = amoxicillin/amoxicillin and D&A/Cefaclor, xlat = Unilateral

+----------------+
| Key            |
|----------------|
|   frequency    |
| row percentage |
+----------------+

           |                    OME at subject level
      Week | No Effusi  R Effusio  L Effusio  Bilateral    Missing |     Total
-----------+-------------------------------------------------------+----------
         0 |         0         74         81          0          0 |       155 
           |      0.00      47.74      52.26       0.00       0.00 |    100.00 
-----------+-------------------------------------------------------+----------
         2 |        52         30         35         21         17 |       155 
           |     33.55      19.35      22.58      13.55      10.97 |    100.00 
-----------+-------------------------------------------------------+----------
         4 |        59         23         33         22         18 |       155 
           |     38.06      14.84      21.29      14.19      11.61 |    100.00 
-----------+-------------------------------------------------------+----------
     Total |       111        127        149         43         35 |       465 
           |     23.87      27.31      32.04       9.25       7.53 |    100.00 
-----------------------------------------------------------------------------
-> trt = amoxicillin/amoxicillin and D&A/Cefaclor, xlat = Bilateral

+----------------+
| Key            |
|----------------|
|   frequency    |
| row percentage |
+----------------+

           |                    OME at subject level
      Week | No Effusi  R Effusio  L Effusio  Bilateral    Missing |     Total
-----------+-------------------------------------------------------+----------
         0 |         0          0          0        351          0 |       351 
           |      0.00       0.00       0.00     100.00       0.00 |    100.00 
-----------+-------------------------------------------------------+----------
```

```
          2 |        78         38         22        195         18 |       351 
            |     22.22      10.83       6.27      55.56       5.13 |    100.00 
------------+-------------------------------------------------------+----------
          4 |        84         27         40        179         21 |       351 
            |     23.93       7.69      11.40      51.00       5.98 |    100.00 
------------+-------------------------------------------------------+----------
      Total |       162         65         62        725         39 |     1,053 
            |     15.38       6.17       5.89      68.85       3.70 |    100.00 


. sort trt xlat2

. by trt xlat2: tab week cat1 if xlat==0, row

-----------------------------------------------------------------------------
-----
-> trt = placebo/D&A/E-S, xlat2 = Unilateral R

+-----------------+
| Key             |
|-----------------|
|   frequency     |
| row percentage  |
+-----------------+

            |                   OME at subject level
       Week | No Effusi  R Effusio  L Effusio  Bilateral    Missing |     Total
------------+-------------------------------------------------------+----------
          0 |         0        128          0          0          0 |       128 
            |      0.00     100.00       0.00       0.00       0.00 |    100.00 
------------+-------------------------------------------------------+----------
          2 |        27         69          3         19         10 |       128 
            |     21.09      53.91       2.34      14.84       7.81 |    100.00 
------------+-------------------------------------------------------+----------
          4 |        41         48          2         26         11 |       128 
            |     32.03      37.50       1.56      20.31       8.59 |    100.00 
------------+-------------------------------------------------------+----------
      Total |        68        245          5         45         21 |       384 
            |     17.71      63.80       1.30      11.72       5.47 |    100.00 

-----------------------------------------------------------------------------
------> trt = placebo/D&A/E-S, xlat2 = Unilateral L

+-----------------+
| Key             |
|-----------------|
|   frequency     |
| row percentage  |
+-----------------+

            |                   OME at subject level
       Week | No Effusi  R Effusio  L Effusio  Bilateral    Missing |     Total
------------+-------------------------------------------------------+----------
          0 |         0          0        131          0          0 |       131 
            |      0.00       0.00     100.00       0.00       0.00 |    100.00 
------------+-------------------------------------------------------+----------
          2 |        26          5         56         29         15 |       131 
```

Week	No Effusi	R Effusio	L Effusio	Bilateral	Missing	Total
	19.85	3.82	42.75	22.14	11.45	100.00
4	39	1	49	27	15	131
	29.77	0.76	37.40	20.61	11.45	100.00
Total	65	6	236	56	30	393
	16.54	1.53	60.05	14.25	7.63	100.00

-> trt = placebo/D&A/E-S, xlat2 = Bilateral
no observations

-> trt = amoxicillin/amoxicillin and D&A/Cefaclor, xlat2 = Unilateral R

```
+----------------+
| Key            |
|----------------|
|   frequency    |
| row percentage |
+----------------+
```

	OME at subject level					
Week	No Effusi	R Effusio	L Effusio	Bilateral	Missing	Total
0	0	74	0	0	0	74
	0.00	100.00	0.00	0.00	0.00	100.00
2	22	30	2	11	9	74
	29.73	40.54	2.70	14.86	12.16	100.00
4	30	19	5	11	9	74
	40.54	25.68	6.76	14.86	12.16	100.00
Total	52	123	7	22	18	222
	23.42	55.41	3.15	9.91	8.11	100.00

-> trt = amoxicillin/amoxicillin and D&A/Cefaclor, xlat2 = Unilateral L

```
+----------------+
| Key            |
|----------------|
|   frequency    |
| row percentage |
+----------------+
```

	OME at subject level					
Week	No Effusi	R Effusio	L Effusio	Bilateral	Missing	Total
0	0	0	81	0	0	81
	0.00	0.00	100.00	0.00	0.00	100.00
2	30	0	33	10	8	81
	37.04	0.00	40.74	12.35	9.88	100.00
4	29	4	28	11	9	81
	35.80	4.94	34.57	13.58	11.11	100.00

```
     Total |        59          4        142         21         17 |       243
           |     24.28       1.65      58.44       8.64       7.00 |    100.00

------------------------------------------------------------------------------------
-----
-> trt = amoxicillin/amoxicillin and D&A/Cefaclor, xlat2 = Bilateral
no observations


.
. * McNemar's test for UL vs. UR by laterality groups
. mcc ome1r ome1l if week==2 & xlat==0

                 | Controls               |
Cases            |   Exposed   Unexposed  |      Total
-----------------+------------------------+------------
         Exposed |        69         104  |        173
       Unexposed |        94         105  |        199
-----------------+------------------------+------------
           Total |       163         209  |        372

McNemar's chi2(1) =      0.51    Prob > chi2 = 0.4773
Exact McNemar significance probability       = 0.5225

Proportion with factor
        Cases       .4650538
        Controls     .438172     [95% Conf. Interval]
                   ---------     --------------------
        difference  .0268817     -.0498936    .103657
        ratio        1.06135      .9006011    1.25079
        rel. diff.  .0478469     -.0809151   .1766089

        odds ratio  1.106383      .8289819   1.478253   (exact)

. mcc ome1r ome1l if week==4 & xlat==0

                 | Controls               |
Cases            |   Exposed   Unexposed  |      Total
-----------------+------------------------+------------
         Exposed |        75          72  |        147
       Unexposed |        84         139  |        223
-----------------+------------------------+------------
           Total |       159         211  |        370

McNemar's chi2(1) =      0.92    Prob > chi2 = 0.3367
Exact McNemar significance probability       = 0.3785

Proportion with factor
        Cases       .3972973
        Controls    .4297297     [95% Conf. Interval]
                   ---------     --------------------
        difference -.0324324     -.1012146   .0363497
        ratio       .9245283      .7877343   1.085077
        rel. diff.  -.056872     -.1761442   .0624001

        odds ratio  .8571429      .6168404   1.188452   (exact)
```

```
.
. mcc ome1r ome1l if week==2 & xlat==1

                 | Controls              |
Cases            |   Exposed   Unexposed |      Total
-----------------+-----------------------+------------
         Exposed |       660          84 |        744
       Unexposed |        75         149 |        224
-----------------+-----------------------+------------
           Total |       735         233 |        968

McNemar's chi2(1) =      0.51    Prob > chi2 = 0.4754
Exact McNemar significance probability       = 0.5259

Proportion with factor
        Cases        .768595
        Controls    .7592975     [95% Conf. Interval]
                   ---------     --------------------
        difference  .0092975       -.01726   .0358551
        ratio       1.012245       .978974   1.046647
        rel. diff.  .0386266     -.0653742   .1426274

        odds ratio      1.12      .8105131   1.550102   (exact)

. mcc ome1r ome1l if week==4 & xlat==1

                 | Controls              |
Cases            |   Exposed   Unexposed |      Total
-----------------+-----------------------+------------
         Exposed |       580          86 |        666
       Unexposed |        91         197 |        288
-----------------+-----------------------+------------
           Total |       671         283 |        954

McNemar's chi2(1) =      0.14    Prob > chi2 = 0.7070
Exact McNemar significance probability       = 0.7638

Proportion with factor
        Cases       .6981132
        Controls    .7033543     [95% Conf. Interval]
                   ---------     --------------------
        difference -.0052411     -.0336202    .023138
        ratio       .9925484       .954578   1.032029
        rel. diff. -.0176678     -.1106183   .0752826

        odds ratio  .9450549      .6955118   1.283234   (exact)

.
. mcc ome1r ome1l if week==2 & trt==0 & xlat==0

                 | Controls              |
Cases            |   Exposed   Unexposed |      Total
-----------------+-----------------------+------------
         Exposed |        48          74 |        122
       Unexposed |        59          53 |        112
-----------------+-----------------------+------------
           Total |       107         127 |        234
```

```
McNemar's chi2(1) =      1.69    Prob > chi2 = 0.1934
Exact McNemar significance probability       = 0.2246

Proportion with factor
        Cases       .5213675
        Controls     .457265     [95% Conf. Interval]
                   ---------     --------------------
        difference  .0641026     -.0364169    .164622
        ratio       1.140187      .9355298   1.389615
        rel. diff.  .1181102     -.0490286   .2852491

        odds ratio  1.254237      .8788323   1.796893   (exact)

. mcc ome1r ome1l if week==2 & trt==1 & xlat==0

                 | Controls               |
Cases            |   Exposed   Unexposed  |      Total
-----------------+------------------------+------------
         Exposed |        21          30  |         51
       Unexposed |        35          52  |         87
-----------------+------------------------+------------
           Total |        56          82  |        138

McNemar's chi2(1) =      0.38    Prob > chi2 = 0.5351
Exact McNemar significance probability       = 0.6201

Proportion with factor
        Cases       .3695652
        Controls    .4057971     [95% Conf. Interval]
                   ---------     --------------------
        difference -.0362319     -.1578239   .0853601
        ratio       .9107143      .6775929    1.22404
        rel. diff. -.0609756     -.2594679   .1375167

        odds ratio  .8571429      .5083432   1.437092   (exact)

. mcc ome1r ome1l if week==4 & trt==0 & xlat==0

                 | Controls               |
Cases            |   Exposed   Unexposed  |      Total
-----------------+------------------------+------------
         Exposed |        53          49  |        102
       Unexposed |        51          80  |        131
-----------------+------------------------+------------
           Total |       104         129  |        233

McNemar's chi2(1) =      0.04    Prob > chi2 = 0.8415
Exact McNemar significance probability       = 0.9204

Proportion with factor
        Cases       .4377682
        Controls    .4463519     [95% Conf. Interval]
                   ---------     --------------------
        difference -.0085837     -.0969869   .0798196
        ratio       .9807692      .8108154   1.186347
        rel. diff. -.0155039     -.1686123   .1376046
```

```
        odds ratio  .9607843      .6357086   1.450762   (exact)

. mcc ome1r ome1l if week==4 & trt==1 & xlat==0

                 | Controls               |
Cases            |   Exposed   Unexposed  |      Total
-----------------+------------------------+------------
         Exposed |        22          23  |         45
       Unexposed |        33          59  |         92
-----------------+------------------------+------------
           Total |        55          82  |        137

McNemar's chi2(1) =      1.79    Prob > chi2 = 0.1814
Exact McNemar significance probability       = 0.2288

Proportion with factor
        Cases       .3284672
        Controls    .4014599     [95% Conf. Interval]
                   ---------     --------------------
        difference -.0729927     -.1866506   .0406652
        ratio       .8181818      .6092729   1.098722
        rel. diff. -.1219512     -.3114102   .0675078

        odds ratio  .6969697      .3907655   1.223384   (exact)

. * transition matrix
. xttrans cat1 if week<4, freq

    OME at |
   subject |                 OME at subject level
     level |         0          1          2          3          4 |    Total
-----------+-------------------------------------------------------+---------
         1 |        49         99          5         30         19 |      202
           |     24.26      49.01       2.48      14.85       9.41 |   100.00
-----------+-------------------------------------------------------+---------
         2 |        56          5         89         39         23 |      212
           |     26.42       2.36      41.98      18.40      10.85 |   100.00
-----------+-------------------------------------------------------+---------
         3 |       149         84         75        660         66 |    1,034
           |     14.41       8.12       7.25      63.83       6.38 |   100.00
-----------+-------------------------------------------------------+---------
     Total |       254        188        169        729        108 |    1,448
           |     17.54      12.98      11.67      50.35       7.46 |    00.00

. xttrans cat1 if week>0, freq

    OME at |
   subject |                 OME at subject level
     level |         0          1          2          3          4 |    Total
-----------+-------------------------------------------------------+---------
         0 |       157         21         29         38          9 |      254
           |     61.81       8.27      11.42      14.96       3.54 |    00.00
-----------+-------------------------------------------------------+---------
         1 |        54         77          8         43          6 |      188
           |     28.72      40.96       4.26      22.87       3.19 |   100.00
-----------+-------------------------------------------------------+---------
```

```
         2 |        44          6         69         43          7 |       169 
           |     26.04       3.55      40.83      25.44       4.14 |    100.00 
-----------+-------------------------------------------------------+----------
         3 |        74         51         68        517         19 |       729 
           |     10.15       7.00       9.33      70.92       2.61 |    100.00 
-----------+-------------------------------------------------------+----------
         4 |         7          3          1         14         83 |       108 
           |      6.48       2.78       0.93      12.96      76.85 |    100.00 
-----------+-------------------------------------------------------+----------
     Total |       336        158        175        655        124 |     1,448 
           |     23.20      10.91      12.09      45.23       8.56 |    100.00 

. sort xlat2

. by xlat2: xttrans cat1 if week>0, freq

-----------------------------------------------------------------------------
-> xlat2 = Unilateral R

    OME at |
   subject |                  OME at subject level
     level |         0          1          2          3          4 |     Total
-----------+-------------------------------------------------------+----------
         0 |        36          6          1          5          1 |        49 
           |     73.47      12.24       2.04      10.20       2.04 |    100.00 
-----------+-------------------------------------------------------+----------
         1 |        29         52          3         13          2 |        99 
           |     29.29      52.53       3.03      13.13       2.02 |    100.00 
-----------+-------------------------------------------------------+----------
         2 |         4          0          1          0          0 |         5 
           |     80.00       0.00      20.00       0.00       0.00 |    100.00 
-----------+-------------------------------------------------------+----------
         3 |         2          6          2         18          2 |        30 
           |      6.67      20.00       6.67      60.00       6.67 |    100.00 
-----------+-------------------------------------------------------+----------
         4 |         0          3          0          1         15 |        19 
           |      0.00      15.79       0.00       5.26      78.95 |    100.00 
-----------+-------------------------------------------------------+----------
     Total |        71         67          7         37         20 |       202 
           |     35.15      33.17       3.47      18.32       9.90 |    100.00 

------------------------------------------------------------------------------
-> xlat2 = Unilateral L

    OME at |
   subject |                  OME at subject level
     level |         0          1          2          3          4 |     Total
-----------+-------------------------------------------------------+----------
         0 |        34          3         14          3          2 |        56 
           |     60.71       5.36      25.00       5.36       3.57 |    100.00 
-----------+-------------------------------------------------------+----------
         1 |         3          0          1          1          0 |         5 
           |     60.00       0.00      20.00      20.00       0.00 |    100.00 
-----------+-------------------------------------------------------+----------
         2 |        22          1         53         10          3 |        89 
           |     24.72       1.12      59.55      11.24       3.37 |    100.00 
-----------+-------------------------------------------------------+----------
```

```
          3 |         5          1          9         24          0 |        39 
            |     12.82       2.56      23.08      61.54       0.00 |    100.00 
------------+-------------------------------------------------------+----------
          4 |         4          0          0          0         19 |        23 
            |     17.39       0.00       0.00       0.00      82.61 |    100.00 
------------+-------------------------------------------------------+----------
      Total |        68          5         77         38         24 |       212 
            |     32.08       2.36      36.32      17.92      11.32 |    100.00 

-------------------------------------------------------------------------------
-> xlat2 = Bilateral

    OME at |
   subject |                 OME at subject level
     level |         0          1          2          3          4 |     Total
------------+-------------------------------------------------------+----------
          0 |        87         12         14         30          6 |       149 
            |     58.39       8.05       9.40      20.13       4.03 |    100.00 
------------+-------------------------------------------------------+----------
          1 |        22         25          4         29          4 |        84 
            |     26.19      29.76       4.76      34.52       4.76 |    100.00 
------------+-------------------------------------------------------+----------
          2 |        18          5         15         33          4 |        75 
            |     24.00       6.67      20.00      44.00       5.33 |    100.00 
------------+-------------------------------------------------------+----------
          3 |        67         44         57        475         17 |       660 
            |     10.15       6.67       8.64      71.97       2.58 |    100.00 
------------+-------------------------------------------------------+----------
          4 |         3          0          1         13         49 |        66 
            |      4.55       0.00       1.52      19.70      74.24 |    100.00 
------------+-------------------------------------------------------+----------
      Total |       197         86         91        580         80 |     1,034 
            |     19.05       8.32       8.80      56.09       7.74 |    100.00 
```

B.2 MODELING

```
. * Baseline
.  xi:  mlogit  cat1  i.study  i.trt  xage  gender  xrace  i.xoccup  xpreab  xuri1
i.durgrp xhxdx i.season if week==0, baseoutcome(1)
i.study          _Istudy_1-3        (naturally coded; _Istudy_1 omitted)
i.trt            _Itrt_0-1          (naturally coded; _Itrt_0 omitted)
i.xoccup         _Ixoccup_1-9       (naturally coded; _Ixoccup_1 omitted)
i.durgrp         _Idurgrp_1-4       (naturally coded; _Idurgrp_1 omitted)
i.season         _Iseason_1-4       (naturally coded; _Iseason_1 omitted)

Iteration 0:   log likelihood = -1010.9842
Iteration 1:   log likelihood = -981.12635
Iteration 2:   log likelihood = -980.34357
Iteration 3:   log likelihood = -980.34207
Iteration 4:   log likelihood = -980.34207
```

```
Multinomial logistic regression                   Number of obs   =       1278
                                                  LR chi2(36)     =      61.28
                                                  Prob > chi2     =     0.0054
Log likelihood = -980.34207                       Pseudo R2       =     0.0303

------------------------------------------------------------------------------
        cat1 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
-
L Effusion   |
   _Istudy_2 |  -.3266058   .3173157    -1.03   0.303   -.9485332    .2953217
   _Istudy_3 |  -.4199986   .3357981    -1.25   0.211   -1.078151    .2381536
     _Itrt_1 |   .3094779   .2800395     1.11   0.269   -.2393895    .8583453
        xage |  -.0417201   .2341626    -0.18   0.859    -.5006703   .4172301
      gender |  -.0734806   .2197366    -0.33   0.738    -.5041564   .3571953
       xrace |    .065982   .2589511     0.25   0.799    -.4415528   .5735168
  _Ixoccup_2 |  -.2479343   .2936802    -0.84   0.399    -.8235369   .3276684
  _Ixoccup_3 |  -.2878265   .2540586    -1.13   0.257    -.7857723   .2101193
  _Ixoccup_9 |   .4099274   .8976054     0.46   0.648    -1.349347   2.169202
      xpreab |   .2124063   .2624547     0.81   0.418    -.3019955   .7268081
       xuri1 |  -.3136263    .266827    -1.18   0.240    -.8365976   .2093449
  _Idurgrp_2 |   .1530066   .3398378     0.45   0.653    -.5130632   .8190764
  _Idurgrp_3 |   .2940532   .3127314     0.94   0.347    -.3188891   .9069956
  _Idurgrp_4 |   .1922431   .3194989     0.60   0.547    -.4339632   .8184494
       xhxdx |   .0133962   .3886291     0.03   0.973    -.7483028   .7750951
  _Iseason_2 |   -.113553    .259654    -0.44   0.662    -.6224655   .3953596
  _Iseason_3 |  -.2747156   .3242709    -0.85   0.397    -.9102749   .3608438
  _Iseason_4 |  -.0763674   .3159946    -0.24   0.809    -.6957053   .5429706
       _cons |   .1213716   .5007615     0.24   0.808    -.8601028   1.102846
-------------+----------------------------------------------------------------
Bilateral    |
   _Istudy_2 |  -.1295532   .2408803    -0.54   0.591      -.60167   .3425635
   _Istudy_3 |   .0833641   .2530736     0.33   0.742    -.4126511   .5793793
     _Itrt_1 |  -.0439525   .2107678    -0.21   0.835    -.4570498   .3691448
        xage |  -.0867264   .1830157    -0.47   0.636    -.4454306   .2719779
      gender |  -.1142711   .1714972    -0.67   0.505    -.4503994   .2218572
       xrace |  -.0899433   .2032854    -0.44   0.658    -.4883752   .3084887
  _Ixoccup_2 |   .1143291   .2264667     0.50   0.614    -.3295376   .5581957
  _Ixoccup_3 |  -.0025196   .1994098    -0.01   0.990    -.3933556   .3883163
  _Ixoccup_9 |   -.706426   .8508732    -0.83   0.406    -2.374107   .9612547
      xpreab |  -.1178181   .2005835    -0.59   0.557    -.5109545   .2753183
       xuri1 |    .438241   .1967711     2.23   0.026     .0525767   .8239053
  _Idurgrp_2 |   .0785698   .2696718     0.29   0.771    -.4499772   .6071167
  _Idurgrp_3 |   .7412059   .2439157     3.04   0.002     .2631399   1.219272
  _Idurgrp_4 |   .5591364   .2452774     2.28   0.023     .0784014   1.039871
       xhxdx |  -.3111074   .2929866    -1.06   0.288    -.8853507   .2631358
  _Iseason_2 |  -.0286123   .2036574    -0.14   0.888    -.4277735    .370549
  _Iseason_3 |  -.3849488   .2520488    -1.53   0.127    -.8789554   .1090578
  _Iseason_4 |    .048414   .2447397     0.20   0.843     -.431267    .528095
       _cons |   1.639332   .3836166     4.27   0.000     .8874568   2.391206
------------------------------------------------------------------------------
(cat1==R Effusion is the base outcome)

.
. testparm _Istudy*
```

```
 ( 1)  [L Effusion]_Istudy_2 = 0
 ( 2)  [Bilateral]_Istudy_2 = 0
 ( 3)  [L Effusion]_Istudy_3 = 0
 ( 4)  [Bilateral]_Istudy_3 = 0

           chi2(  4) =    4.56
         Prob > chi2 =    0.3360

. testparm _Itrt*

 ( 1)  [L Effusion]_Itrt_1 = 0
 ( 2)  [Bilateral]_Itrt_1 = 0

           chi2(  2) =    2.49
         Prob > chi2 =    0.2880

. testparm xage

 ( 1)  [L Effusion]xage = 0
 ( 2)  [Bilateral]xage = 0

           chi2(  2) =    0.25
         Prob > chi2 =    0.8829

. testparm gender

 ( 1)  [L Effusion]gender = 0
 ( 2)  [Bilateral]gender = 0

           chi2(  2) =    0.46
         Prob > chi2 =    0.7951

. testparm xrace

 ( 1)  [L Effusion]xrace = 0
 ( 2)  [Bilateral]xrace = 0

           chi2(  2) =    0.67
         Prob > chi2 =    0.7137

. testparm _Ixoccup*

 ( 1)  [L Effusion]_Ixoccup_2 = 0
 ( 2)  [Bilateral]_Ixoccup_2 = 0
 ( 3)  [L Effusion]_Ixoccup_3 = 0
 ( 4)  [Bilateral]_Ixoccup_3 = 0
 ( 5)  [L Effusion]_Ixoccup_9 = 0
 ( 6)  [Bilateral]_Ixoccup_9 = 0

           chi2(  6) =    7.12
         Prob > chi2 =    0.3098

. testparm xpreab

 ( 1)  [L Effusion]xpreab = 0
 ( 2)  [Bilateral]xpreab = 0
```

```
           chi2(  2) =    2.70
         Prob > chi2 =    0.2589

. testparm xuri1

 ( 1)  [L Effusion]xuri1 = 0
 ( 2)  [Bilateral]xuri1 = 0

           chi2(  2) =   15.71
         Prob > chi2 =    0.0004

. testparm _Idurgrp*

 ( 1)  [L Effusion]_Idurgrp_2 = 0
 ( 2)  [Bilateral]_Idurgrp_2 = 0
 ( 3)  [L Effusion]_Idurgrp_3 = 0
 ( 4)  [Bilateral]_Idurgrp_3 = 0
 ( 5)  [L Effusion]_Idurgrp_4 = 0
 ( 6)  [Bilateral]_Idurgrp_4 = 0

           chi2(  6) =   16.35
         Prob > chi2 =    0.0120

. testparm xhxdx

 ( 1)  [L Effusion]xhxdx = 0
 ( 2)  [Bilateral]xhxdx = 0

           chi2(  2) =    2.01
         Prob > chi2 =    0.3667

. testparm _Iseason*

 ( 1)  [L Effusion]_Iseason_2 = 0
 ( 2)  [Bilateral]_Iseason_2 = 0
 ( 3)  [L Effusion]_Iseason_3 = 0
 ( 4)  [Bilateral]_Iseason_3 = 0
 ( 5)  [L Effusion]_Iseason_4 = 0
 ( 6)  [Bilateral]_Iseason_4 = 0

           chi2(  6) =    3.37
         Prob > chi2 =    0.7618

.
. xi: mlogit cat1 xuri1 i.durgrp if week==0, baseoutcome(1)
i.durgrp          _Idurgrp_1-4        (naturally coded; _Idurgrp_1 omitted)

Iteration 0:   log likelihood = -1021.1356
Iteration 1:   log likelihood = -1003.4503
Iteration 2:   log likelihood = -1003.2452
Iteration 3:   log likelihood = -1003.2451

Multinomial logistic regression                   Number of obs   =       1289
                                                  LR chi2(8)      =      35.78
                                                  Prob > chi2     =     0.0000
Log likelihood = -1003.2451                       Pseudo R2       =     0.0175
```

```
------------------------------------------------------------------------------
        cat1 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
-
L Effusion   |
       xuri1 |  -.2384627   .2610409    -0.91   0.361    -.7500934     .273168
  _Idurgrp_2 |    .218595   .3320431     0.66   0.510    -.4321976    .8693876
  _Idurgrp_3 |   .3496523   .3038706     1.15   0.250    -.2459232    .9452278
  _Idurgrp_4 |   .1349241   .2988336     0.45   0.652     -.450779    .7206273
       _cons |  -.1308602   .2400394    -0.55   0.586    -.6013287    .3396083
-------------+----------------------------------------------------------------
Bilateral    |
       xuri1 |   .4838889   .1930911     2.51   0.012     .1054372    .8623406
  _Idurgrp_2 |   .0662502    .262331     0.25   0.801    -.4479091    .5804094
  _Idurgrp_3 |   .7363836   .2368323     3.11   0.002     .2722008    1.200566
  _Idurgrp_4 |   .6058358   .2292334     2.64   0.008     .1565467    1.055125
       _cons |    1.05003   .1867319     5.62   0.000     .6840426    1.416018
------------------------------------------------------------------------------
-
(cat1==R Effusion is the base outcome)

.
. testparm xuri1

 ( 1)  [L Effusion]xuri1 = 0
 ( 2)  [Bilateral]xuri1 = 0

           chi2(  2) =   16.64
         Prob > chi2 =    0.0002

. testparm _Idurgrp*

 ( 1)  [L Effusion]_Idurgrp_2 = 0
 ( 2)  [Bilateral]_Idurgrp_2 = 0
 ( 3)  [L Effusion]_Idurgrp_3 = 0
 ( 4)  [Bilateral]_Idurgrp_3 = 0
 ( 5)  [L Effusion]_Idurgrp_4 = 0
 ( 6)  [Bilateral]_Idurgrp_4 = 0

           chi2(  6) =   20.50
         Prob > chi2 =    0.0023

.
. mlogit, rrr

Multinomial logistic regression                   Number of obs   =       1289
                                                  LR chi2(8)      =      35.78
                                                  Prob > chi2     =     0.0000
Log likelihood = -1003.2451                       Pseudo R2       =     0.0175

------------------------------------------------------------------------------
        cat1 |        RRR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
L Effusion   |
       xuri1 |   .7878381    .205658    -0.91   0.361     .4723224    1.314121
  _Idurgrp_2 |   1.244327   .4131703     0.66  0.510     .6490811     2.38545
  _Idurgrp_3 |   1.418574   .4310631     1.15   0.250     .7819823      2.5734
```

```
  _Idurgrp_4 |    1.14445   .3420001     0.45   0.652    .6371316    2.055722
-------------+----------------------------------------------------------------
Bilateral    |
       xuri1 |   1.622371   .3132656     2.51   0.012    1.111196    2.368698
  _Idurgrp_2 |   1.068494   .2802991     0.25   0.801    .6389627     1.78677
  _Idurgrp_3 |   2.088369   .4945934     3.11   0.002    1.312851    3.321998
  _Idurgrp_4 |   1.832783   .4201352     2.64   0.008    1.169465    2.872334
------------------------------------------------------------------------------
(cat1==R Effusion is the base outcome)

.
. test ["L Effusion"]

 ( 1)  [L Effusion]xuri1 = 0
 ( 2)  [L Effusion]_Idurgrp_2 = 0
 ( 3)  [L Effusion]_Idurgrp_3 = 0
 ( 4)  [L Effusion]_Idurgrp_4 = 0

           chi2(  4) =    2.30
         Prob > chi2 =    0.6809

. test ["Bilateral"]

 ( 1)  [Bilateral]xuri1 = 0
 ( 2)  [Bilateral]_Idurgrp_2 = 0
 ( 3)  [Bilateral]_Idurgrp_3 = 0
 ( 4)  [Bilateral]_Idurgrp_4 = 0

           chi2(  4) =   19.54
         Prob > chi2 =    0.0006

. test ["Bilateral"="L Effusion"]

 ( 1) - [L Effusion]xuri1 + [Bilateral]xuri1 = 0
 ( 2) - [L Effusion]_Idurgrp_2 + [Bilateral]_Idurgrp_2 = 0
 ( 3) - [L Effusion]_Idurgrp_3 + [Bilateral]_Idurgrp_3 = 0
 ( 4) - [L Effusion]_Idurgrp_4 + [Bilateral]_Idurgrp_4 = 0

           chi2(  4) =   20.06
         Prob > chi2 =    0.0005

.
. * 2 week prevalance
.
.  xi:  mlogit  cat1  i.study  i.trt  xage  gender  xrace  i.xoccup  xpreab  xuri1
i.durgrp xhxdx i.season if week==2, baseoutcome(0)
i.study           _Istudy_1-3         (naturally coded; _Istudy_1 omitted)
i.trt             _Itrt_0-1           (naturally coded; _Itrt_0 omitted)
i.xoccup          _Ixoccup_1-9        (naturally coded; _Ixoccup_1 omitted)
i.durgrp          _Idurgrp_1-4        (naturally coded; _Idurgrp_1 omitted)
i.season          _Iseason_1-4        (naturally coded; _Iseason_1 omitted)

Iteration 0:   log likelihood = -1746.2784
Iteration 1:   log likelihood = -1677.9654
Iteration 2:   log likelihood = -1676.1854
Iteration 3:   log likelihood = -1676.1805
Iteration 4:   log likelihood = -1676.1805
```

```
Multinomial logistic regression                   Number of obs   =       1278
                                                  LR chi2(72)     =     140.20
                                                  Prob > chi2     =     0.0000
Log likelihood = -1676.1805                       Pseudo R2       =     0.0401

------------------------------------------------------------------------------
        cat1 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
R Effusion   |
   _Istudy_2 |  -.2666786   .3168154    -0.84   0.400    -.8876255    .3542682
   _Istudy_3 |  -.3163391   .3268568    -0.97   0.333    -.9569667    .3242884
     _Itrt_1 |  -.3516485    .270001    -1.30   0.193    -.8808407    .1775438
        xage |  -.1436523   .2305428    -0.62   0.533     -.595508    .3082034
      gender |  -.1139956   .2131241    -0.53   0.593    -.5317111      .30372
       xrace |  -.2134859   .2559894    -0.83   0.404    -.7152158    .2882441
  _Ixoccup_2 |  -.4677047   .2839918    -1.65   0.100    -1.024318     .088909
  _Ixoccup_3 |   .2615856   .2476344     1.06   0.291    -.2237689      .74694
  _Ixoccup_9 |   .4422744   .9494211     0.47   0.641    -1.418557    2.303105
      xpreab |  -.2180859   .2472626    -0.88   0.378    -.7027116    .2665398
       xuri1 |   .0202813   .2382512     0.09   0.932    -.4466824     .487245
  _Idurgrp_2 |   .7943135   .3453359     2.30   0.021     .1174677    1.471159
  _Idurgrp_3 |   .8910571   .3120621     2.86   0.004     .2794266    1.502688
  _Idurgrp_4 |    .201098   .3135255     0.64   0.521    -.4134008    .8155967
       xhxdx |  -.4727423   .3442505    -1.37   0.170    -1.147461    .2019763
  _Iseason_2 |   .0701368   .2520713     0.28   0.781    -.4239138    .5641874
  _Iseason_3 |   .1949751   .3155931     0.62   0.537    -.4235761    .8135262
  _Iseason_4 |   .1714658   .3032769     0.57   0.572    -.4229461    .7658777
       _cons |   .2211369   .4640584     0.48   0.634    -.6884009    1.130675
-------------+----------------------------------------------------------------
L Effusion   |
   _Istudy_2 |  -.4086945   .3315987    -1.23   0.218    -1.058616    .2412269
   _Istudy_3 |  -.2562349   .3336171    -0.77   0.442    -.9101124    .3976426
     _Itrt_1 |  -.3701104   .2812888    -1.32   0.188    -.9214263    .1812055
        xage |  -.0737871   .2389289    -0.31   0.757    -.5420792     .394505
      gender |  -.2888404   .2200343    -1.31   0.189    -.7200997    .1424189
       xrace |  -.1397552   .2658701    -0.53   0.599     -.660851    .3813407
  _Ixoccup_2 |  -.5060425   .3027308    -1.67   0.095    -1.099384    .0872989
  _Ixoccup_3 |   .3520906   .2568772     1.37   0.170    -.1513794    .8555605
  _Ixoccup_9 |   .2731664   1.034307     0.26   0.792    -1.754039    2.300371
      xpreab |  -.0688955   .2599732    -0.27   0.791    -.5784335    .4406426
       xuri1 |  -.4288336   .2683466    -1.60   0.110    -.9547832     .097116
  _Idurgrp_2 |   .6459045   .3551781     1.82   0.069    -.0502319    1.342041
  _Idurgrp_3 |    .642293   .3240168     1.98   0.047     .0072318    1.277354
  _Idurgrp_4 |   .2195487   .3198733     0.69   0.492    -.4073915    .8464889
       xhxdx |  -.1655254   .3761734    -0.44   0.660    -.9028118    .5717609
  _Iseason_2 |   .1658084   .2641657     0.63   0.530    -.3519468    .6835636
  _Iseason_3 |   .3048027   .3272938     0.93   0.352    -.3366814    .9462868
  _Iseason_4 |   .3109944   .3169119     0.98   0.326    -.3101415    .9321303
       _cons |  -.0787156    .494065    -0.16   0.873    -1.047065     .889634
-------------+----------------------------------------------------------------
Bilateral    |
   _Istudy_2 |   -.192361   .2443104    -0.79   0.431    -.6712006    .2864787
   _Istudy_3 |  -.1579513    .249235    -0.63   0.526    -.6464428    .3305403
     _Itrt_1 |  -.7303797   .2017792    -3.62   0.000     -1.12586   -.3348997
        xage |  -.1689183    .175218    -0.96   0.335    -.5123392    .1745026
      gender |  -.0620549   .1642723    -0.38   0.706    -.3840228    .2599129
```

```
       xrace |  -.1906943   .1974838    -0.97   0.334   -.5777553    .1963668
  _Ixoccup_2 |   .0093937   .2024523     0.05   0.963   -.3874055    .4061928
  _Ixoccup_3 |    .348516   .1956506     1.78   0.075   -.0349521    .7319841
  _Ixoccup_9 |  -.8877551    .948797    -0.94   0.349   -2.747363    .9718528
      xpreab |  -.0247227   .1919914    -0.13   0.898    -.401019    .3515736
       xuri1 |   .2913974   .1811195     1.61   0.108   -.0635903    .6463851
  _Idurgrp_2 |   .3659574   .2699976     1.36   0.175   -.1632281     .895143
  _Idurgrp_3 |   1.081087   .2343069     4.61   0.000    .6218536     1.54032
  _Idurgrp_4 |   .5429701   .2286121     2.38   0.018    .0948986    .9910416
       xhxdx |  -.2696527    .281476    -0.96   0.338   -.8213355      .28203
  _Iseason_2 |   .0969818   .1910517     0.51   0.612   -.2774726    .4714363
  _Iseason_3 |  -.2287067   .2534924    -0.90   0.367   -.7255427    .2681292
  _Iseason_4 |   .2233055   .2320258     0.96   0.336   -.2314567    .6780678
       _cons |   1.024077   .3663569     2.80   0.005    .3060307    1.742123
-------------+----------------------------------------------------------------
Missing      |
   _Istudy_2 |   .1470763   .3625824     0.41   0.685    -.563572    .8577247
   _Istudy_3 |   -.312565    .395095    -0.79   0.429   -1.086937    .4618069
     _Itrt_1 |  -.8479389   .3212027    -2.64   0.008   -1.477485   -.2183932
        xage |    .076687   .2763242     0.28   0.781   -.4648986    .6182725
      gender |  -.7612529   .2538164    -3.00   0.003   -1.258724   -.2637818
       xrace |   -.025847   .2992943    -0.09   0.931    -.612453     .560759
  _Ixoccup_2 |   .7147196   .3478763     2.05   0.040    .0328946    1.396545
  _Ixoccup_3 |    1.06024   .3274765     3.24   0.001    .4183977    1.702082
  _Ixoccup_9 |   1.281759   1.070631     1.20   0.231   -.8166396    3.380158
      xpreab |  -.2446252   .2978151    -0.82   0.411   -.8283322    .3390817
       xuri1 |  -.1142923   .2924275    -0.39   0.696   -.6874396    .4588551
  _Idurgrp_2 |    .771939   .4920167     1.57   0.117   -.1923961    1.736274
  _Idurgrp_3 |   1.530271   .4196545     3.65   0.000     .707763    2.352779
  _Idurgrp_4 |   .9135816    .417099     2.19   0.029    .0960826    1.731081
       xhxdx |  -.3557718   .4058132    -0.88   0.381   -1.151151    .4396076
  _Iseason_2 |   .1457251   .3007787     0.48   0.628   -.4437904    .7352405
  _Iseason_3 |  -.0308465    .398575    -0.08   0.938   -.8120392    .7503462
  _Iseason_4 |   .0279763   .3731991     0.07   0.940   -.7034805    .7594332
       _cons |  -1.245374   .5904962    -2.11   0.035   -2.402725   -.0880221
------------------------------------------------------------------------------
(cat1==No Effusion is the base outcome)

.
. testparm _Istudy*

 ( 1)  [R Effusion]_Istudy_2 = 0
 ( 2)  [L Effusion]_Istudy_2 = 0
 ( 3)  [Bilateral]_Istudy_2 = 0
 ( 4)  [Missing]_Istudy_2 = 0
 ( 5)  [R Effusion]_Istudy_3 = 0
 ( 6)  [L Effusion]_Istudy_3 = 0
 ( 7)  [Bilateral]_Istudy_3 = 0
 ( 8)  [Missing]_Istudy_3 = 0

           chi2(  8) =    4.80
         Prob > chi2 =    0.7791

. testparm _Itrt*

 ( 1)  [R Effusion]_Itrt_1 = 0
 ( 2)  [L Effusion]_Itrt_1 = 0
```

```
 ( 3)  [Bilateral]_Itrt_1 = 0
 ( 4)  [Missing]_Itrt_1 = 0

           chi2(  4) =   15.58
         Prob > chi2 =    0.0036

. testparm xage

 ( 1)  [R Effusion]xage = 0
 ( 2)  [L Effusion]xage = 0
 ( 3)  [Bilateral]xage = 0
 ( 4)  [Missing]xage = 0

           chi2(  4) =    1.68
         Prob > chi2 =    0.7950

. testparm gender

 ( 1)  [R Effusion]gender = 0
 ( 2)  [L Effusion]gender = 0
 ( 3)  [Bilateral]gender = 0
 ( 4)  [Missing]gender = 0

           chi2(  4) =   11.39
         Prob > chi2 =    0.0226

. testparm xrace

 ( 1)  [R Effusion]xrace = 0
 ( 2)  [L Effusion]xrace = 0
 ( 3)  [Bilateral]xrace = 0
 ( 4)  [Missing]xrace = 0

           chi2(  4) =    1.30
         Prob > chi2 =    0.8608

. testparm _Ixoccup*

 ( 1)  [R Effusion]_Ixoccup_2 = 0
 ( 2)  [L Effusion]_Ixoccup_2 = 0
 ( 3)  [Bilateral]_Ixoccup_2 = 0
 ( 4)  [Missing]_Ixoccup_2 = 0
 ( 5)  [R Effusion]_Ixoccup_3 = 0
 ( 6)  [L Effusion]_Ixoccup_3 = 0
 ( 7)  [Bilateral]_Ixoccup_3 = 0
 ( 8)  [Missing]_Ixoccup_3 = 0
 ( 9)  [R Effusion]_Ixoccup_9 = 0
 (10)  [L Effusion]_Ixoccup_9 = 0
 (11)  [Bilateral]_Ixoccup_9 = 0
 (12)  [Missing]_Ixoccup_9 = 0

           chi2( 12) =   25.47
         Prob > chi2 =    0.0127

. testparm xpreab

 ( 1)  [R Effusion]xpreab = 0
```

```
 ( 2)  [L Effusion]xpreab = 0
 ( 3)  [Bilateral]xpreab = 0
 ( 4)  [Missing]xpreab = 0

           chi2(  4) =    1.56
         Prob > chi2 =    0.8163

. testparm xuri1

 ( 1)  [R Effusion]xuri1 = 0
 ( 2)  [L Effusion]xuri1 = 0
 ( 3)  [Bilateral]xuri1 = 0
 ( 4)  [Missing]xuri1 = 0

           chi2(  4) =   11.82
         Prob > chi2 =    0.0187

. testparm _Idurgrp*

 ( 1)  [R Effusion]_Idurgrp_2 = 0
 ( 2)  [L Effusion]_Idurgrp_2 = 0
 ( 3)  [Bilateral]_Idurgrp_2 = 0
 ( 4)  [Missing]_Idurgrp_2 = 0
 ( 5)  [R Effusion]_Idurgrp_3 = 0
 ( 6)  [L Effusion]_Idurgrp_3 = 0
 ( 7)  [Bilateral]_Idurgrp_3 = 0
 ( 8)  [Missing]_Idurgrp_3 = 0
 ( 9)  [R Effusion]_Idurgrp_4 = 0
 (10)  [L Effusion]_Idurgrp_4 = 0
 (11)  [Bilateral]_Idurgrp_4 = 0
 (12)  [Missing]_Idurgrp_4 = 0

           chi2( 12) =   37.32
         Prob > chi2 =    0.0002

. testparm xhxdx

 ( 1)  [R Effusion]xhxdx = 0
 ( 2)  [L Effusion]xhxdx = 0
 ( 3)  [Bilateral]xhxdx = 0
 ( 4)  [Missing]xhxdx = 0

           chi2(  4) =    2.10
         Prob > chi2 =    0.7174

. testparm _Iseason*

 ( 1)  [R Effusion]_Iseason_2 = 0
 ( 2)  [L Effusion]_Iseason_2 = 0
 ( 3)  [Bilateral]_Iseason_2 = 0
 ( 4)  [Missing]_Iseason_2 = 0
 ( 5)  [R Effusion]_Iseason_3 = 0
 ( 6)  [L Effusion]_Iseason_3 = 0
 ( 7)  [Bilateral]_Iseason_3 = 0
 ( 8)  [Missing]_Iseason_3 = 0
 ( 9)  [R Effusion]_Iseason_4 = 0
 (10)  [L Effusion]_Iseason_4 = 0
```

```
 (11)  [Bilateral]_Iseason_4 = 0
 (12)  [Missing]_Iseason_4 = 0

           chi2( 12) =    7.27
         Prob > chi2 =    0.8390

.
.  xi:  mlogit  cat1  i.trt  gender  i.xoccup  xuri1  i.durgrp  if  week==2,
baseoutcome(0)
i.trt             _Itrt_0-1           (naturally coded; _Itrt_0 omitted)
i.xoccup          _Ixoccup_1-9        (naturally coded; _Ixoccup_1 omitted)
i.durgrp          _Idurgrp_1-4        (naturally coded; _Idurgrp_1 omitted)

Iteration 0:   log likelihood = -1765.6059
Iteration 1:   log likelihood = -1708.0461
Iteration 2:   log likelihood =  -1706.773
Iteration 3:   log likelihood = -1706.7711
Iteration 4:   log likelihood = -1706.7711

Multinomial logistic regression                   Number of obs   =       1289
                                                  LR chi2(36)     =     117.67
                                                  Prob > chi2     =     0.0000
Log likelihood = -1706.7711                       Pseudo R2       =     0.0333

------------------------------------------------------------------------------
        cat1 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
R Effusion   |
      _Itrt_1 |  -.6031388   .2063041    -2.92   0.003    -1.007487   -.1987901
       gender |  -.0917704    .209794    -0.44   0.662    -.5029591    .3194184
   _Ixoccup_2 |  -.4884226   .2813728    -1.74   0.083    -1.039903    .0630579
   _Ixoccup_3 |    .217727   .2308118     0.94   0.346    -.2346559    .6701098
   _Ixoccup_9 |   .5142936   .9425162     0.55   0.585    -1.333004    2.361591
        xuri1 |   .0293513   .2323613     0.13   0.899    -.4260685    .4847711
   _Idurgrp_2 |   .6726568   .3334342     2.02   0.044     .0191377    1.326176
   _Idurgrp_3 |   .8052972   .3026036     2.66   0.008     .2122051    1.398389
   _Idurgrp_4 |   .2975909   .2954263     1.01   0.314    -.2814339    .8766157
        _cons |  -.4196105   .3136685    -1.34   0.181    -1.034389    .1951684
-------------+----------------------------------------------------------------
L Effusion   |
      _Itrt_1 |  -.6212685   .2166741    -2.87   0.004     -1.045942   -.196595
       gender |  -.2875832   .2176747    -1.32   0.186    -.7142178    .1390514
   _Ixoccup_2 |   -.510772   .3006108    -1.70   0.089    -1.099958    .0784144
   _Ixoccup_3 |   .2707202    .240702     1.12   0.261     -.201047    .7424875
   _Ixoccup_9 |   .2991354   1.027285     0.29   0.771    -1.714307    2.312578
        xuri1 |  -.4472464   .2641429    -1.69   0.090     -.964957    .0704643
   _Idurgrp_2 |   .5732574   .3475399     1.65   0.099    -.1079084    1.254423
   _Idurgrp_3 |   .6018009   .3175614     1.90   0.058     -.020608     1.22421
   _Idurgrp_4 |   .2601769   .3037005     0.86   0.392    -.3350653     .855419
        _cons |  -.2726923   .3197654    -0.85   0.394     -.899421    .3540364
-------------+----------------------------------------------------------------
Bilateral    |
      _Itrt_1 |  -.8713042   .1580383    -5.51   0.000    -1.181054   -.5615547
       gender |  -.0834276   .1621589    -0.51   0.607    -.4012533    .2343981
   _Ixoccup_2 |   .0018624   .2004758     0.01   0.993    -.3910629    .3947877
   _Ixoccup_3 |   .2619508   .1831986     1.43   0.153    -.0971119    .6210135
   _Ixoccup_9 |  -.5214347    .900103    -0.58   0.562    -2.285604    1.242735
```

```
       xuri1 |   .2954098   .1775371     1.66   0.096   -.0525566    .6433761
  _Idurgrp_2 |   .3260269   .2632685     1.24   0.216   -.1899698    .8420236
  _Idurgrp_3 |   1.065826   .2293075     4.65   0.000    .6163913     1.51526
  _Idurgrp_4 |   .5963474   .2169385     2.75   0.006    .1711557    1.021539
       _cons |   .6705327   .2388081     2.81   0.005    .2024774    1.138588
-------------+----------------------------------------------------------------
Missing      |
     _Itrt_1 |  -.8152927   .2544209    -3.20   0.001   -1.313948   -.3166369
      gender |  -.7702711   .2482571    -3.10   0.002   -1.256846   -.2836961
  _Ixoccup_2 |   .6795027   .3383971     2.01   0.045    .0162565    1.342749
  _Ixoccup_3 |   1.064437   .3052617     3.49   0.000    .4661347    1.662739
  _Ixoccup_9 |   1.204511   1.057181     1.14   0.255   -.8675254    3.276547
       xuri1 |    -.00443    .280201    -0.02   0.987   -.5536138    .5447539
  _Idurgrp_2 |   .5250913   .4725949     1.11   0.267   -.4011777     1.45136
  _Idurgrp_3 |   1.354882   .3984125     3.40   0.001    .5740077    2.135756
  _Idurgrp_4 |   .8898677   .3880606     2.29   0.022     .129283    1.650452
       _cons |     -1.552   .4290825    -3.62   0.000   -2.392987    -.711014
------------------------------------------------------------------------------
(cat1==No Effusion is the base outcome)

.
. testparm _Itrt*

 ( 1)  [R Effusion]_Itrt_1 = 0
 ( 2)  [L Effusion]_Itrt_1 = 0
 ( 3)  [Bilateral]_Itrt_1 = 0
 ( 4)  [Missing]_Itrt_1 = 0

           chi2(  4) =   31.10
         Prob > chi2 =    0.0000

. testparm gender

 ( 1)  [R Effusion]gender = 0
 ( 2)  [L Effusion]gender = 0
 ( 3)  [Bilateral]gender = 0
 ( 4)  [Missing]gender = 0

           chi2(  4) =   11.80
         Prob > chi2 =    0.0189

. testparm _Ixoccup*

 ( 1)  [R Effusion]_Ixoccup_2 = 0
 ( 2)  [L Effusion]_Ixoccup_2 = 0
 ( 3)  [Bilateral]_Ixoccup_2 = 0
 ( 4)  [Missing]_Ixoccup_2 = 0
 ( 5)  [R Effusion]_Ixoccup_3 = 0
 ( 6)  [L Effusion]_Ixoccup_3 = 0
 ( 7)  [Bilateral]_Ixoccup_3 = 0
 ( 8)  [Missing]_Ixoccup_3 = 0
 ( 9)  [R Effusion]_Ixoccup_9 = 0
 (10)  [L Effusion]_Ixoccup_9 = 0
 (11)  [Bilateral]_Ixoccup_9 = 0
 (12)  [Missing]_Ixoccup_9 = 0

           chi2( 12) =   25.24
```

```
         Prob > chi2 =    0.0137

. testparm xuri1

 ( 1)  [R Effusion]xuri1 = 0
 ( 2)  [L Effusion]xuri1 = 0
 ( 3)  [Bilateral]xuri1 = 0
 ( 4)  [Missing]xuri1 = 0

           chi2(  4) =   12.14
         Prob > chi2 =    0.0163

. testparm _Idurgrp*

 ( 1)  [R Effusion]_Idurgrp_2 = 0
 ( 2)  [L Effusion]_Idurgrp_2 = 0
 ( 3)  [Bilateral]_Idurgrp_2 = 0
 ( 4)  [Missing]_Idurgrp_2 = 0
 ( 5)  [R Effusion]_Idurgrp_3 = 0
 ( 6)  [L Effusion]_Idurgrp_3 = 0
 ( 7)  [Bilateral]_Idurgrp_3 = 0
 ( 8)  [Missing]_Idurgrp_3 = 0
 ( 9)  [R Effusion]_Idurgrp_4 = 0
 (10)  [L Effusion]_Idurgrp_4 = 0
 (11)  [Bilateral]_Idurgrp_4 = 0
 (12)  [Missing]_Idurgrp_4 = 0

           chi2( 12) =   35.80
         Prob > chi2 =    0.0003

.
. mlogit, rrr

Multinomial logistic regression                   Number of obs   =       1289
                                                  LR chi2(36)     =     117.67
                                                  Prob > chi2     =     0.0000
Log likelihood = -1706.7711                       Pseudo R2       =     0.0333

------------------------------------------------------------------------------
        cat1 |        RRR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
R Effusion   |
     _Itrt_1 |   .5470917   .1128673    -2.92   0.003     .3651352    .8197219
      gender |   .9123146   .1913982    -0.44   0.662     .6047385    1.376327
  _Ixoccup_2 |   .6135935   .1726485    -1.74   0.083     .3534889    1.065088
  _Ixoccup_3 |   1.243248   .2869562     0.94   0.346     .7908429    1.954452
  _Ixoccup_9 |   1.672457   1.576317     0.55   0.585     .2636839    10.60782
       xuri1 |   1.029786   .2392825     0.13   0.899     .6530716    1.623803
  _Idurgrp_2 |   1.959436   .6533431     2.02   0.044     1.019322    3.766612
  _Idurgrp_3 |   2.237361   .6770336     2.66   0.008     1.236401    4.048674
  _Idurgrp_4 |   1.346611   .3978242     1.01   0.314     .7547008    2.402754
-------------+----------------------------------------------------------------
L Effusion   |
     _Itrt_1 |   .5372625   .1164109    -2.87   0.004     .3513607    .8215233
      gender |   .7500742   .1632722    -1.32   0.186     .4895749    1.149183
  _Ixoccup_2 |   .6000322   .1803762    -1.70   0.089     .3328849    1.081571
  _Ixoccup_3 |   1.310908   .3155382     1.12   0.261      .817874    2.101156
```

```
   _Ixoccup_9 |   1.348692   1.385492     0.29   0.771    .1800885    10.10043
        xuri1 |   .6393864   .1688894    -1.69   0.090    .3809996    1.073006
   _Idurgrp_2 |   1.774036   .6165485     1.65   0.099    .8977098    3.505816
   _Idurgrp_3 |   1.825403   .5796776     1.90   0.058    .9796029    3.401477
   _Idurgrp_4 |   1.297159    .393948     0.86   0.392    .7152914     2.35236
-------------+----------------------------------------------------------------
Bilateral     |
      _Itrt_1 |   .4184055   .0661241    -5.51   0.000    .3069552    .5703217
       gender |   .9199577   .1491794    -0.51   0.607    .6694805    1.264148
   _Ixoccup_2 |   1.001864   .2008495     0.01   0.993    .6763376    1.484069
   _Ixoccup_3 |   1.299463   .2380598     1.43   0.153    .9074545    1.860813
   _Ixoccup_9 |   .5936682   .5343625    -0.58   0.562    .1017126    3.465077
        xuri1 |   1.343677   .2385525     1.66   0.096    .9488006    1.902894
   _Idurgrp_2 |   1.385453    .364746     1.24   0.216    .8269841    2.321059
   _Idurgrp_3 |   2.903236   .6657337     4.65   0.000    1.852232    4.550605
   _Idurgrp_4 |   1.815475   .3938465     2.75   0.006    1.186676    2.777466
-------------+----------------------------------------------------------------
Missing       |
      _Itrt_1 |   .4425098   .1125837    -3.20   0.001    .2687568    .7285952
       gender |   .4628876   .1149151    -3.10   0.002    .2845501    .7529954
   _Ixoccup_2 |   1.972896   .6676225     2.01   0.045    1.016389    3.829556
   _Ixoccup_3 |   2.899205   .8850165     3.49   0.000    1.593822    5.273734
   _Ixoccup_9 |   3.335126   3.525831     1.14   0.255    .4199896    26.48415
        xuri1 |   .9955798   .2789625    -0.02   0.987    .5748686    1.724184
   _Idurgrp_2 |   1.690613   .7989752     1.11   0.267    .6695311    4.268918
   _Idurgrp_3 |   3.876303   1.544367     3.40   0.001    1.775368    8.463442
   _Idurgrp_4 |   2.434808   .9448528     2.29   0.022    1.138012    5.209336
------------------------------------------------------------------------------
(cat1==No Effusion is the base outcome)

.
. test ["R Effusion"="L Effusion"]

 ( 1)  [R Effusion]_Itrt_1 - [L Effusion]_Itrt_1 = 0
 ( 2)  [R Effusion]gender - [L Effusion]gender = 0
 ( 3)  [R Effusion]_Ixoccup_2 - [L Effusion]_Ixoccup_2 = 0
 ( 4)  [R Effusion]_Ixoccup_3 - [L Effusion]_Ixoccup_3 = 0
 ( 5)  [R Effusion]_Ixoccup_9 - [L Effusion]_Ixoccup_9 = 0
 ( 6)  [R Effusion]xuri1 - [L Effusion]xuri1 = 0
 ( 7)  [R Effusion]_Idurgrp_2 - [L Effusion]_Idurgrp_2 = 0
 ( 8)  [R Effusion]_Idurgrp_3 - [L Effusion]_Idurgrp_3 = 0
 ( 9)  [R Effusion]_Idurgrp_4 - [L Effusion]_Idurgrp_4 = 0

           chi2(  9) =    4.43
         Prob > chi2 =    0.8808

.
. * 4 week prevalance
.
.  xi:  mlogit  cat1  i.study  i.trt  xage  gender  xrace  i.xoccup  xpreab  xuri1
i.durgrp xhxdx i.season if week==4, baseoutcome(0)
i.study           _Istudy_1-3         (naturally coded; _Istudy_1 omitted)
i.trt             _Itrt_0-1           (naturally coded; _Itrt_0 omitted)
i.xoccup          _Ixoccup_1-9        (naturally coded; _Ixoccup_1 omitted)
i.durgrp          _Idurgrp_1-4        (naturally coded; _Idurgrp_1 omitted)
i.season          _Iseason_1-4        (naturally coded; _Iseason_1 omitted)
```

Iteration 0: log likelihood = -1798.418
Iteration 1: log likelihood = -1719.6928
Iteration 2: log likelihood = -1718.1626
Iteration 3: log likelihood = -1718.1594
Iteration 4: log likelihood = -1718.1594

Multinomial logistic regression

Number of obs = 1278
LR chi2(72) = 160.52
Prob > chi2 = 0.0000
Log likelihood = -1718.1594
Pseudo R2 = 0.0446

cat1	Coef.	Std. Err.	z	P>|z|	95% Conf.	Interval]
R Effusion						
_Istudy_2	.1951617	.3062143	0.64	0.524	-.4050073	.7953307
_Istudy_3	-.7610933	.3413166	-2.23	0.026	-1.430062	-.092125
_Itrt_1	-.548281	.285136	-1.92	0.054	-1.107137	.0105753
xage	-.3068702	.2374475	-1.29	0.196	-.7722587	.1585183
gender	-.0812659	.2158054	-0.38	0.706	-.5042367	.3417049
xrace	-.258948	.2578933	-1.00	0.315	-.7644096	.2465136
_Ixoccup_2	-.3221918	.2827519	-1.14	0.255	-.8763754	.2319918
_Ixoccup_3	-.0364199	.2453153	-0.15	0.882	-.517229	.4443892
_Ixoccup_9	-1.106282	1.142828	-0.97	0.333	-3.346183	1.133619
xpreab	.0422876	.2464108	0.17	0.864	-.4406687	.5252439
xuri1	-.010055	.2375433	-0.04	0.966	-.4756314	.4555213
_Idurgrp_2	.2053585	.3383606	0.61	0.544	-.4578161	.8685331
_Idurgrp_3	.5220581	.3147353	1.66	0.097	-.0948117	1.138928
_Idurgrp_4	-.096572	.3199535	-0.30	0.763	-.7236693	.5305253
xhxdx	-.2134335	.3258737	-0.65	0.512	-.8521343	.4252672
_Iseason_2	.0350658	.2493702	0.14	0.888	-.4536908	.5238224
_Iseason_3	-.2071401	.3144187	-0.66	0.510	-.8233893	.4091092
_Iseason_4	-.1318095	.3182243	-0.41	0.679	-.7555178	.4918987
_cons	-.0892839	.4557021	-0.20	0.845	-.9824436	.8038757
L Effusion						
_Istudy_2	.5560416	.3143087	1.77	0.077	-.0599922	1.172075
_Istudy_3	.3173566	.3154421	1.01	0.314	-.3008987	.9356118
_Itrt_1	-.3040333	.2597039	-1.17	0.242	-.8130436	.204977
xage	-.0607895	.2284526	-0.27	0.790	-.5085485	.3869694
gender	-.0516811	.2132771	-0.24	0.809	-.4696965	.3663343
xrace	-.1439865	.2610353	-0.55	0.581	-.6556064	.3676333
_Ixoccup_2	-.7213614	.2904292	-2.48	0.013	-1.290592	-.1521307
_Ixoccup_3	-.1382339	.2413278	-0.57	0.567	-.6112277	.33476
_Ixoccup_9	.0033671	.903775	0.00	0.997	-1.767999	1.774733
xpreab	.3128424	.248642	1.26	0.208	-.1744869	.8001717
xuri1	-.062667	.2415703	-0.26	0.795	-.5361362	.4108021
_Idurgrp_2	-.5555795	.3712449	-1.50	0.135	-1.283206	.1720472
_Idurgrp_3	.6503567	.2973743	2.19	0.029	.0675138	1.2332
_Idurgrp_4	.0450227	.3071523	0.15	0.883	-.5569848	.6470303
xhxdx	.4720987	.4085883	1.16	0.248	-.3287196	1.272917
_Iseason_2	.0223646	.2473207	0.09	0.928	-.4623751	.5071043
_Iseason_3	-.1257183	.3055165	-0.41	0.681	-.7245196	.4730831
_Iseason_4	.0125948	.3150946	0.04	0.968	-.6049793	.6301689
_cons	-1.34485	.5226188	-2.57	0.010	-2.369164	-.3205355
Bilateral						

```
   _Istudy_2 |   .4420491   .2250553     1.96   0.050     .0009489    .8831493
   _Istudy_3 |   .2279728   .2238416     1.02   0.308    -.2107487    .6666943
     _Itrt_1 |  -.7080764   .1938629    -3.65   0.000    -1.088041   -.3281121
        xage |  -.0233333   .1646464    -0.14   0.887    -.3460344    .2993677
      gender |  -.2605757   .1524461    -1.71   0.087    -.5593646    .0382132
       xrace |  -.0336177   .1818595    -0.18   0.853    -.3900558    .3228205
  _Ixoccup_2 |   -.030945   .1928741    -0.16   0.873    -.4089714    .3470814
  _Ixoccup_3 |   .0948915   .1796877     0.53   0.597      -.25729     .447073
  _Ixoccup_9 |  -1.131758   .7893724    -1.43   0.152    -2.678899    .4153835
      xpreab |   .0106409    .176443     0.06   0.952     -.335181    .3564628
       xuri1 |   .2082541   .1679953     1.24   0.215    -.1210106    .5375188
  _Idurgrp_2 |  -.0711794   .2513081    -0.28   0.777    -.5637343    .4213754
  _Idurgrp_3 |   .9053314   .2264268     4.00   0.000     .4615429     1.34912
  _Idurgrp_4 |   .3902808   .2208506     1.77   0.077    -.0425784    .8231399
       xhxdx |  -.0352536    .239992    -0.15   0.883    -.5056293    .4351222
  _Iseason_2 |  -.3066437   .1786813    -1.72   0.086    -.6568527    .0435653
  _Iseason_3 |  -.9662009   .2375143    -4.07   0.000     -1.43172   -.5006813
  _Iseason_4 |   .1034584   .2140859     0.48   0.629    -.3161423     .523059
       _cons |   .6280943   .3334631     1.88   0.060    -.0254814     1.28167
-------------+----------------------------------------------------------------
Missing      |
   _Istudy_2 |   .2974053   .3398492     0.88   0.382    -.3686869    .9634975
   _Istudy_3 |  -.1131057   .3563445    -0.32   0.751    -.8115281    .5853167
     _Itrt_1 |  -.5899203   .3099201    -1.90   0.057    -1.197353    .0175119
        xage |   .2585245   .2540088     1.02   0.309    -.2393236    .7563725
      gender |  -.8576556   .2331468    -3.68   0.000    -1.314615   -.4006962
       xrace |   .2078907   .2726068     0.76   0.446    -.3264089    .7421903
  _Ixoccup_2 |   .0476085   .3163709     0.15   0.880    -.5724671    .6676841
  _Ixoccup_3 |    .263818    .284772     0.93   0.354    -.2943248    .8219608
  _Ixoccup_9 |   .2434752   .9217532     0.26   0.792    -1.563128    2.050078
      xpreab |  -.5269033   .2702844    -1.95   0.051    -1.056651    .0028444
       xuri1 |   .0306737   .2625626     0.12   0.907    -.4839394    .5452869
  _Idurgrp_2 |   .1197822   .4283175     0.28   0.780    -.7197047    .9592691
  _Idurgrp_3 |   .9626344   .3669064     2.62   0.009      .243511    1.681758
  _Idurgrp_4 |   .3822149   .3600921     1.06   0.288    -.3235527    1.087983
       xhxdx |  -.1571468   .3412917    -0.46   0.645    -.8260662    .5117727
  _Iseason_2 |  -.0774872   .2809064    -0.28   0.783    -.6280537    .4730792
  _Iseason_3 |   -.293638    .350196    -0.84   0.402    -.9800095    .3927335
  _Iseason_4 |   .0055277   .3417465     0.02   0.987    -.6642831    .6753386
       _cons |  -.6194064   .4972471    -1.25   0.213    -1.593993    .3551799
------------------------------------------------------------------------------
(cat1==No Effusion is the base outcome)

.
. testparm _Istudy*

 ( 1)  [R Effusion]_Istudy_2 = 0
 ( 2)  [L Effusion]_Istudy_2 = 0
 ( 3)  [Bilateral]_Istudy_2 = 0
 ( 4)  [Missing]_Istudy_2 = 0
 ( 5)  [R Effusion]_Istudy_3 = 0
 ( 6)  [L Effusion]_Istudy_3 = 0
 ( 7)  [Bilateral]_Istudy_3 = 0
 ( 8)  [Missing]_Istudy_3 = 0

           chi2(  8) =   16.51
         Prob > chi2 =    0.0356
```

```
. testparm _Itrt*

 ( 1)  [R Effusion]_Itrt_1 = 0
 ( 2)  [L Effusion]_Itrt_1 = 0
 ( 3)  [Bilateral]_Itrt_1 = 0
 ( 4)  [Missing]_Itrt_1 = 0

           chi2(  4) =   14.30
         Prob > chi2 =    0.0064

. testparm xage

 ( 1)  [R Effusion]xage = 0
 ( 2)  [L Effusion]xage = 0
 ( 3)  [Bilateral]xage = 0
 ( 4)  [Missing]xage = 0

           chi2(  4) =    3.80
         Prob > chi2 =    0.4338

. testparm gender

 ( 1)  [R Effusion]gender = 0
 ( 2)  [L Effusion]gender = 0
 ( 3)  [Bilateral]gender = 0
 ( 4)  [Missing]gender = 0

           chi2(  4) =   15.22
         Prob > chi2 =    0.0043

. testparm xrace

 ( 1)  [R Effusion]xrace = 0
 ( 2)  [L Effusion]xrace = 0
 ( 3)  [Bilateral]xrace = 0
 ( 4)  [Missing]xrace = 0

           chi2(  4) =    2.52
         Prob > chi2 =    0.6415

. testparm _Ixoccup*

 ( 1)  [R Effusion]_Ixoccup_2 = 0
 ( 2)  [L Effusion]_Ixoccup_2 = 0
 ( 3)  [Bilateral]_Ixoccup_2 = 0
 ( 4)  [Missing]_Ixoccup_2 = 0
 ( 5)  [R Effusion]_Ixoccup_3 = 0
 ( 6)  [L Effusion]_Ixoccup_3 = 0
 ( 7)  [Bilateral]_Ixoccup_3 = 0
 ( 8)  [Missing]_Ixoccup_3 = 0
 ( 9)  [R Effusion]_Ixoccup_9 = 0
 (10)  [L Effusion]_Ixoccup_9 = 0
 (11)  [Bilateral]_Ixoccup_9 = 0
 (12)  [Missing]_Ixoccup_9 = 0

           chi2( 12) =   13.05
```

```
         Prob > chi2 =    0.3654

. testparm xpreab

 ( 1)  [R Effusion]xpreab = 0
 ( 2)  [L Effusion]xpreab = 0
 ( 3)  [Bilateral]xpreab = 0
 ( 4)  [Missing]xpreab = 0

           chi2(  4) =    7.70
         Prob > chi2 =    0.1034

. testparm xuri1

 ( 1)  [R Effusion]xuri1 = 0
 ( 2)  [L Effusion]xuri1 = 0
 ( 3)  [Bilateral]xuri1 = 0
 ( 4)  [Missing]xuri1 = 0

           chi2(  4) =    2.91
         Prob > chi2 =    0.5730

. testparm _Idurgrp*

 ( 1)  [R Effusion]_Idurgrp_2 = 0
 ( 2)  [L Effusion]_Idurgrp_2 = 0
 ( 3)  [Bilateral]_Idurgrp_2 = 0
 ( 4)  [Missing]_Idurgrp_2 = 0
 ( 5)  [R Effusion]_Idurgrp_3 = 0
 ( 6)  [L Effusion]_Idurgrp_3 = 0
 ( 7)  [Bilateral]_Idurgrp_3 = 0
 ( 8)  [Missing]_Idurgrp_3 = 0
 ( 9)  [R Effusion]_Idurgrp_4 = 0
 (10)  [L Effusion]_Idurgrp_4 = 0
 (11)  [Bilateral]_Idurgrp_4 = 0
 (12)  [Missing]_Idurgrp_4 = 0

           chi2( 12) =   34.12
         Prob > chi2 =    0.0006

. testparm xhxdx

 ( 1)  [R Effusion]xhxdx = 0
 ( 2)  [L Effusion]xhxdx = 0
 ( 3)  [Bilateral]xhxdx = 0
 ( 4)  [Missing]xhxdx = 0

           chi2(  4) =    2.67
         Prob > chi2 =    0.6142

. testparm _Iseason*

 ( 1)  [R Effusion]_Iseason_2 = 0
 ( 2)  [L Effusion]_Iseason_2 = 0
 ( 3)  [Bilateral]_Iseason_2 = 0
 ( 4)  [Missing]_Iseason_2 = 0
 ( 5)  [R Effusion]_Iseason_3 = 0
```

```
 ( 6)  [L Effusion]_Iseason_3 = 0
 ( 7)  [Bilateral]_Iseason_3 = 0
 ( 8)  [Missing]_Iseason_3 = 0
 ( 9)  [R Effusion]_Iseason_4 = 0
 (10)  [L Effusion]_Iseason_4 = 0
 (11)  [Bilateral]_Iseason_4 = 0
 (12)  [Missing]_Iseason_4 = 0

           chi2( 12) =   26.60
         Prob > chi2 =    0.0088

.
. xi: mlogit cat1 i.study i.trt gender xpreab i.durgrp i.season if week==4,
baseoutcome(0)
i.study           _Istudy_1-3         (naturally coded; _Istudy_1 omitted)
i.trt             _Itrt_0-1           (naturally coded; _Itrt_0 omitted)
i.durgrp          _Idurgrp_1-4        (naturally coded; _Idurgrp_1 omitted)
i.season          _Iseason_1-4        (naturally coded; _Iseason_1 omitted)

Iteration 0:   log likelihood = -2033.5652
Iteration 1:   log likelihood =  -1970.776
Iteration 2:   log likelihood = -1970.1764
Iteration 3:   log likelihood = -1970.1761

Multinomial logistic regression                   Number of obs   =       1447
                                                  LR chi2(44)     =     126.78
                                                  Prob > chi2     =     0.0000
Log likelihood = -1970.1761                       Pseudo R2       =     0.0312

------------------------------------------------------------------------------
        cat1 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
R Effusion   |
   _Istudy_2 |   .3204294   .2897053     1.11   0.269    -.2473826    .8882413
   _Istudy_3 |  -.6339116   .3256641    -1.95   0.052    -1.272202    .0043784
     _Itrt_1 |  -.5653623   .2799959    -2.02   0.043    -1.114144   -.0165804
      gender |   -.053475   .2024629    -0.26   0.792     -.450295     .343345
      xpreab |   .0324947   .2260265     0.14   0.886    -.4105092    .4754986
  _Idurgrp_2 |   .3239877   .3153306     1.03   0.304    -.2940488    .9420243
  _Idurgrp_3 |   .4911009   .2949424     1.67   0.096    -.0869755    1.069177
  _Idurgrp_4 |   .1041938   .3005717     0.35   0.729    -.4849159    .6933035
  _Iseason_2 |   .0533525   .2422445     0.22   0.826     -.421438     .528143
  _Iseason_3 |  -.2461952   .2974723    -0.83   0.408    -.8292303    .3368398
  _Iseason_4 |  -.0746118   .2829233    -0.26   0.792    -.6291313    .4799077
       _cons |  -.7305878   .3584198    -2.04   0.042    -1.433078   -.0280979
-------------+----------------------------------------------------------------
L Effusion   |
   _Istudy_2 |   .3682657   .2884373     1.28   0.202    -.1970609    .9335924
   _Istudy_3 |   .1458801   .2856768     0.51   0.610    -.4140362    .7057963
     _Itrt_1 |   -.274636   .2560479    -1.07   0.283    -.7764806    .2272086
      gender |   .0048001   .1964401     0.02   0.981    -.3802154    .3898157
      xpreab |   .3339904   .2230053     1.50   0.134     -.103092    .7710728
  _Idurgrp_2 |  -.3561894   .3332918    -1.07   0.285    -1.009429    .2970505
  _Idurgrp_3 |   .6704794   .2720631     2.46   0.014     .1372456    1.203713
  _Idurgrp_4 |   .1303494   .2821896     0.46   0.644    -.4227321    .6834308
  _Iseason_2 |   .0216623   .2348704     0.09   0.927    -.4386752    .4819999
  _Iseason_3 |  -.1058932   .2818412    -0.38   0.707    -.6582917    .4465054
```

```
  _Iseason_4 |   .0399995   .2754321     0.15   0.885   -.4998375    .5798365
       _cons |  -1.133116   .3532477    -3.21   0.001   -1.825469   -.4407632
-------------+----------------------------------------------------------------
Bilateral    |
   _Istudy_2 |   .4012663    .211297     1.90   0.058   -.0128681    .8154008
   _Istudy_3 |   .1838344   .2070339     0.89   0.375   -.2219445    .5896133
     _Itrt_1 |  -.7298874   .1915311    -3.81   0.000   -1.105282   -.3544933
      gender |  -.2246491   .1420977    -1.58   0.114   -.5031553    .0538572
      xpreab |  -.0377255    .158605    -0.24   0.812   -.3485855    .2731345
  _Idurgrp_2 |   .0930868   .2324927     0.40   0.689   -.3625906    .5487641
  _Idurgrp_3 |   .9000117   .2085019     4.32   0.000    .4913555    1.308668
  _Idurgrp_4 |   .4564431   .2064398     2.21   0.027    .0518285    .8610576
  _Iseason_2 |  -.3182565   .1718704    -1.85   0.064   -.6551164    .0186033
  _Iseason_3 |  -.9746243   .2204031    -4.42   0.000   -1.406606    -.542642
  _Iseason_4 |   .0681364    .192727     0.35   0.724   -.3096015    .4458743
       _cons |   .6700936    .250041     2.68   0.007    .1800222    1.160165
-------------+----------------------------------------------------------------
Missing      |
   _Istudy_2 |   .2606257    .318916     0.82   0.414   -.3644382    .8856897
   _Istudy_3 |  -.2516273    .329679    -0.76   0.445   -.8977861    .3945316
     _Itrt_1 |  -.5315543   .3031693    -1.75   0.080   -1.125755    .0626465
      gender |  -.7512688   .2154735    -3.49   0.000   -1.173589   -.3289484
      xpreab |  -.4438642    .237903    -1.87   0.062   -.9101454    .0224171
  _Idurgrp_2 |  -.0584642   .3952548    -0.15   0.882   -.8331493     .716221
  _Idurgrp_3 |   .7675294   .3279405     2.34   0.019    .1247778    1.410281
  _Idurgrp_4 |   .3152641   .3295921     0.96   0.339   -.3307246    .9612528
  _Iseason_2 |  -.0457499   .2654894    -0.17   0.863   -.5660996    .4745997
  _Iseason_3 |  -.2922473   .3209323    -0.91   0.362    -.921263    .3367684
  _Iseason_4 |  -.0990324   .3091151    -0.32   0.749   -.7048867     .506822
       _cons |   -.416881   .3791642    -1.10   0.272   -1.160029    .3262672
------------------------------------------------------------------------------
(cat1==No Effusion is the base outcome)

.
. testparm _Istudy*

 ( 1)  [R Effusion]_Istudy_2 = 0
 ( 2)  [L Effusion]_Istudy_2 = 0
 ( 3)  [Bilateral]_Istudy_2 = 0
 ( 4)  [Missing]_Istudy_2 = 0
 ( 5)  [R Effusion]_Istudy_3 = 0
 ( 6)  [L Effusion]_Istudy_3 = 0
 ( 7)  [Bilateral]_Istudy_3 = 0
 ( 8)  [Missing]_Istudy_3 = 0

           chi2(  8) =   15.12
         Prob > chi2 =    0.0569

. testparm _Itrt*

 ( 1)  [R Effusion]_Itrt_1 = 0
 ( 2)  [L Effusion]_Itrt_1 = 0
 ( 3)  [Bilateral]_Itrt_1 = 0
 ( 4)  [Missing]_Itrt_1 = 0

           chi2(  4) =   15.74
         Prob > chi2 =    0.0034
```

```
. testparm gender

 ( 1)  [R Effusion]gender = 0
 ( 2)  [L Effusion]gender = 0
 ( 3)  [Bilateral]gender = 0
 ( 4)  [Missing]gender = 0

           chi2(  4) =   14.47
         Prob > chi2 =    0.0059

. testparm xpreab

 ( 1)  [R Effusion]xpreab = 0
 ( 2)  [L Effusion]xpreab = 0
 ( 3)  [Bilateral]xpreab = 0
 ( 4)  [Missing]xpreab = 0

           chi2(  4) =    8.41
         Prob > chi2 =    0.0776

. testparm _Idurgrp*

 ( 1)  [R Effusion]_Idurgrp_2 = 0
 ( 2)  [L Effusion]_Idurgrp_2 = 0
 ( 3)  [Bilateral]_Idurgrp_2 = 0
 ( 4)  [Missing]_Idurgrp_2 = 0
 ( 5)  [R Effusion]_Idurgrp_3 = 0
 ( 6)  [L Effusion]_Idurgrp_3 = 0
 ( 7)  [Bilateral]_Idurgrp_3 = 0
 ( 8)  [Missing]_Idurgrp_3 = 0
 ( 9)  [R Effusion]_Idurgrp_4 = 0
 (10)  [L Effusion]_Idurgrp_4 = 0
 (11)  [Bilateral]_Idurgrp_4 = 0
 (12)  [Missing]_Idurgrp_4 = 0

           chi2( 12) =   32.63
         Prob > chi2 =    0.0011

. testparm _Iseason*

 ( 1)  [R Effusion]_Iseason_2 = 0
 ( 2)  [L Effusion]_Iseason_2 = 0
 ( 3)  [Bilateral]_Iseason_2 = 0
 ( 4)  [Missing]_Iseason_2 = 0
 ( 5)  [R Effusion]_Iseason_3 = 0
 ( 6)  [L Effusion]_Iseason_3 = 0
 ( 7)  [Bilateral]_Iseason_3 = 0
 ( 8)  [Missing]_Iseason_3 = 0
 ( 9)  [R Effusion]_Iseason_4 = 0
 (10)  [L Effusion]_Iseason_4 = 0
 (11)  [Bilateral]_Iseason_4 = 0
 (12)  [Missing]_Iseason_4 = 0

           chi2( 12) =   31.61
         Prob > chi2 =    0.0016
```

```
.
. mlogit, rrr

Multinomial logistic regression                   Number of obs   =       1447
                                                  LR chi2(44)     =     126.78
                                                  Prob > chi2     =     0.0000
Log likelihood = -1970.1761                       Pseudo R2       =     0.0312

------------------------------------------------------------------------------
        cat1 |        RRR   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
R Effusion   |
   _Istudy_2 |   1.377719   .3991325     1.11   0.269     .7808419    2.430851
   _Istudy_3 |   .5305126   .1727689    -1.95   0.052      .280214    1.004388
     _Itrt_1 |   .5681543   .1590809    -2.02   0.043     .3281961    .9835563
      gender |   .9479296   .1919206    -0.26   0.792     .6374401    1.409655
      xpreab |   1.033028   .2334918     0.14   0.886     .6633124    1.608816
  _Idurgrp_2 |    1.38263   .4359856     1.03   0.304     .7452401    2.565169
  _Idurgrp_3 |   1.634114   .4819695     1.67   0.096     .9166995    2.912982
  _Idurgrp_4 |   1.109816   .3335791     0.35   0.729      .615749    2.000313
  _Iseason_2 |   1.054801   .2555198     0.22   0.826     .6561027     1.69578
  _Iseason_3 |   .7817696   .2325548    -0.83   0.408      .436385    1.400515
  _Iseason_4 |   .9281037   .2625822    -0.26   0.792     .5330547    1.615925
-------------+----------------------------------------------------------------
L Effusion   |
   _Istudy_2 |   1.445226    .416857     1.28   0.202     .8211406     2.54363
   _Istudy_3 |   1.157057   .3305445     0.51   0.610      .660977    2.025459
     _Itrt_1 |   .7598486   .1945576    -1.07   0.283     .4600222    1.255092
      gender |   1.004812   .1973853     0.02   0.981     .6837141    1.476709
      xpreab |    1.39653   .3114336     1.50   0.134      .902044    2.162085
  _Idurgrp_2 |     .70034   .2334176    -1.07   0.285     .3644269    1.345883
  _Idurgrp_3 |   1.955174   .5319307     2.46   0.014      1.14711    3.332468
  _Idurgrp_4 |   1.139226   .3214778     0.46   0.644     .6552541    1.980661
  _Iseason_2 |   1.021899   .2400138     0.09   0.927     .6448902     1.61931
  _Iseason_3 |   .8995207    .253522    -0.38   0.707      .517735    1.562841
  _Iseason_4 |    1.04081   .2866725     0.15   0.885     .6066292    1.785746
-------------+----------------------------------------------------------------
Bilateral    |
   _Istudy_2 |   1.493715   .3156175     1.90   0.058     .9872143    2.260081
   _Istudy_3 |   1.201817   .2488168     0.89   0.375     .8009598    1.803291
     _Itrt_1 |   .4819633    .092311    -3.81   0.000     .3311177    .7015288
      gender |   .7987965   .1135071    -1.58   0.114     .6046199    1.055334
      xpreab |   .9629772    .152733    -0.24   0.812     .7056855    1.314077
  _Idurgrp_2 |   1.097557    .255174     0.40   0.689     .6958713    1.731112
  _Idurgrp_3 |   2.459632   .5128378     4.32   0.000      1.63453     3.70124
  _Idurgrp_4 |    1.57845   .3258548     2.21   0.027     1.053195    2.365661
  _Iseason_2 |   .7274161   .1250213    -1.85   0.064     .5193816    1.018777
  _Iseason_3 |   .3773341   .0831656    -4.42   0.000     .2449732    .5812106
  _Iseason_4 |   1.070511   .2063164     0.35   0.724     .7337393    1.561855
-------------+----------------------------------------------------------------
Missing      |
   _Istudy_2 |   1.297742   .4138707     0.82   0.414     .6945868    2.424656
   _Istudy_3 |   .7775345   .2563368    -0.76   0.445     .4074708    1.483689
     _Itrt_1 |   .5876908   .1781698    -1.75   0.080     .3244074     1.06465
      gender |   .4717676   .1016534    -3.49   0.000      .309255    .7196801
      xpreab |   .6415526   .1526273    -1.87   0.062     .4024657     1.02267
  _Idurgrp_2 |    .943212   .3728091    -0.15   0.882     .4346782    2.046684
```

```
  _Idurgrp_3 |   2.154437   .7065272     2.34   0.019    1.132897    4.097107
  _Idurgrp_4 |   1.370621    .451746     0.96   0.339     .718403    2.614971
  _Iseason_2 |   .9552808   .2536169    -0.17   0.863    .5677355    1.607371
  _Iseason_3 |   .7465839   .2396029    -0.91   0.362     .398016    1.400415
  _Iseason_4 |   .9057134   .2799697    -0.32   0.749    .4941645    1.660007
------------------------------------------------------------------------------
(cat1==No Effusion is the base outcome)
.
. test ["L Effusion"="R Effusion"]

 ( 1) - [R Effusion]_Istudy_2 + [L Effusion]_Istudy_2 = 0
 ( 2) - [R Effusion]_Istudy_3 + [L Effusion]_Istudy_3 = 0
 ( 3) - [R Effusion]_Itrt_1 + [L Effusion]_Itrt_1 = 0
 ( 4) - [R Effusion]gender + [L Effusion]gender = 0
 ( 5) - [R Effusion]xpreab + [L Effusion]xpreab = 0
 ( 6) - [R Effusion]_Idurgrp_2 + [L Effusion]_Idurgrp_2 = 0
 ( 7) - [R Effusion]_Idurgrp_3 + [L Effusion]_Idurgrp_3 = 0
 ( 8) - [R Effusion]_Idurgrp_4 + [L Effusion]_Idurgrp_4 = 0
 ( 9) - [R Effusion]_Iseason_2 + [L Effusion]_Iseason_2 = 0
 (10) - [R Effusion]_Iseason_3 + [L Effusion]_Iseason_3 = 0
 (11) - [R Effusion]_Iseason_4 + [L Effusion]_Iseason_4 = 0

           chi2( 11) =   18.24
         Prob > chi2 =    0.0762

.
. * 0-2 week regression
. xi: mlogit cat1 i.cat1p i.study i.trt xage gender i.xoccup xpreab xuri1
i.durgrp xhxdx i.season ///
> if week==2, baseoutcome(0)
i.cat1p           _Icat1p_0-4         (naturally coded; _Icat1p_0 omitted)
i.study           _Istudy_1-3         (naturally coded; _Istudy_1 omitted)
i.trt             _Itrt_0-1           (naturally coded; _Itrt_0 omitted)
i.xoccup          _Ixoccup_1-9        (naturally coded; _Ixoccup_1 omitted)
i.durgrp          _Idurgrp_1-4        (naturally coded; _Idurgrp_1 omitted)
i.season          _Iseason_1-4        (naturally coded; _Iseason_1 omitted)

note: _Icat1p_1 dropped due to collinearity
note: _Icat1p_4 dropped due to collinearity
Iteration 0:   log likelihood = -1762.1827
Iteration 1:   log likelihood = -1537.5732
Iteration 2:   log likelihood = -1483.2296
Iteration 3:   log likelihood =  -1479.113
Iteration 4:   log likelihood =  -1479.105
Iteration 5:   log likelihood =  -1479.105

Multinomial logistic regression                   Number of obs   =       1286
                                                  LR chi2(76)     =     566.16
                                                  Prob > chi2     =     0.0000
Log likelihood =  -1479.105                       Pseudo R2       =     0.1606

------------------------------------------------------------------------------
        cat1 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
R Effusion   |
   _Icat1p_2 |  -3.091649   .5122849    -6.04   0.000   -4.095709    -2.08759
   _Icat1p_3 |  -1.413134   .2446118    -5.78   0.000   -1.892564   -.9337038
```

_Istudy_2	-.3238264	.3326766	-0.97	0.330	-.9758606	.3282078
_Istudy_3	-.3476495	.3378664	-1.03	0.304	-1.009855	.3145564
_Itrt_1	-.28178	.2849347	-0.99	0.323	-.8402417	.2766817
xage	-.1869932	.2399912	-0.78	0.436	-.6573673	.283381
gender	-.1277665	.224583	-0.57	0.569	-.567941	.312408
_Ixoccup_2	-.5443306	.2998862	-1.82	0.070	-1.132097	.0434356
_Ixoccup_3	.0937043	.2496967	0.38	0.707	-.3956922	.5831008
_Ixoccup_9	.5783531	1.008537	0.57	0.566	-1.398343	2.555049
xpreab	-.2319092	.2607808	-0.89	0.374	-.7430303	.2792118
xuri1	.0814888	.2499278	0.33	0.744	-.4083608	.5713384
_Idurgrp_2	.918852	.3667337	2.51	0.012	.2000672	1.637637
_Idurgrp_3	1.118998	.3346236	3.34	0.001	.4631482	1.774849
_Idurgrp_4	.3664098	.3335983	1.10	0.272	-.2874308	1.02025
xhxdx	-.5877235	.3589794	-1.64	0.102	-1.29131	.1158632
_Iseason_2	.0070403	.2665801	0.03	0.979	-.515447	.5295276
_Iseason_3	.0458532	.329758	0.14	0.889	-.6004606	.692167
_Iseason_4	.1655286	.3157119	0.52	0.600	-.4532555	.7843126
_cons	1.335876	.5123235	2.61	0.009	.3317398	2.340011
L Effusion						
_Icat1p_2	3.567228	.7498237	4.76	0.000	2.097601	5.036856
_Icat1p_3	2.362657	.7409887	3.19	0.001	.9103461	3.814968
_Istudy_2	-.2716505	.3462544	-0.78	0.433	-.9502967	.4069957
_Istudy_3	-.0615	.3477672	-0.18	0.860	-.7431112	.6201111
_Itrt_1	-.5048956	.2942708	-1.72	0.086	-1.081656	.0718646
xage	-.0571605	.2468351	-0.23	0.817	-.5409484	.4266273
gender	-.2887381	.229365	-1.26	0.208	-.7382852	.160809
_Ixoccup_2	-.4108015	.3153065	-1.30	0.193	-1.028791	.2071879
_Ixoccup_3	.39989	.2570329	1.56	0.120	-.1038852	.9036651
_Ixoccup_9	-.1100874	1.086169	-0.10	0.919	-2.23894	2.018765
xpreab	-.1446101	.2741305	-0.53	0.598	-.681896	.3926758
xuri1	-.3643427	.2782302	-1.31	0.190	-.9096638	.1809784
_Idurgrp_2	.5431039	.3717434	1.46	0.144	-.1854997	1.271707
_Idurgrp_3	.5395238	.3397585	1.59	0.112	-.1263906	1.205438
_Idurgrp_4	.2058679	.3366821	0.61	0.541	-.4540169	.8657527
xhxdx	-.1642768	.3913225	-0.42	0.675	-.9312548	.6027012
_Iseason_2	.2096597	.2751864	0.76	0.446	-.3296957	.749015
_Iseason_3	.3460709	.3425005	1.01	0.312	-.3252178	1.01736
_Iseason_4	.2983292	.328818	0.91	0.364	-.3461423	.9428007
_cons	-2.782093	.8846482	-3.14	0.002	-4.515972	-1.048215
Bilateral						
_Icat1p_2	.0135859	.3430502	0.04	0.968	-.6587802	.6859519
_Icat1p_3	1.839287	.2682262	6.86	0.000	1.313573	2.365
_Istudy_2	-.1641133	.2518639	-0.65	0.515	-.6577576	.3295309
_Istudy_3	-.2085184	.2542674	-0.82	0.412	-.7068734	.2898365
_Itrt_1	-.7567701	.2088836	-3.62	0.000	-1.166174	-.3473658
xage	-.1785835	.1794015	-1.00	0.320	-.530204	.173037
gender	-.0035659	.1691146	-0.02	0.983	-.3350244	.3278925
_Ixoccup_2	-.0442819	.2100544	-0.21	0.833	-.4559809	.3674171
_Ixoccup_3	.224813	.1927345	1.17	0.243	-.1529397	.6025657
_Ixoccup_9	-.7798662	.987827	-0.79	0.430	-2.715971	1.156239
xpreab	.0677697	.1974441	0.34	0.731	-.3192137	.454753
xuri1	.1206184	.1862066	0.65	0.517	-.2443398	.4855766
_Idurgrp_2	.2881116	.2808737	1.03	0.305	-.2623907	.8386139
_Idurgrp_3	.9207919	.2430027	3.79	0.000	.4445154	1.397068
_Idurgrp_4	.4271835	.2379389	1.80	0.073	-.0391681	.8935351

```
       xhxdx |  -.1791647    .286609    -0.63   0.532    -.740908    .3825785
  _Iseason_2 |   .0761671   .1976465     0.39   0.700   -.3112128    .4635471
  _Iseason_3 |  -.2677244   .2598567    -1.03   0.303   -.7770341    .2415854
  _Iseason_4 |   .1715427   .2376294     0.72   0.470   -.2942025    .6372878
       _cons |  -.4057563   .4442725    -0.91   0.361   -1.276514    .4650018
-------------+----------------------------------------------------------------
Missing      |
   _Icat1p_2 |  -.0039921   .4023393    -0.01   0.992   -.7925627    .7845784
   _Icat1p_3 |  -.1081183    .332719    -0.32   0.745   -.7602356     .543999
   _Istudy_2 |   .1505917   .3623048     0.42   0.678   -.5595127    .8606961
   _Istudy_3 |  -.2790215   .3876966    -0.72   0.472   -1.038893    .4808499
     _Itrt_1 |  -.8217846   .3200116    -2.57   0.010   -1.448996   -.1945735
        xage |   .1446808   .2668658     0.54   0.588   -.3783664    .6677281
      gender |   -.782679   .2514989    -3.11   0.002   -1.275608   -.2897502
  _Ixoccup_2 |   .7314016   .3433201     2.13   0.033    .0585066    1.404296
  _Ixoccup_3 |   .9965457   .3114546     3.20   0.001     .386106    1.606985
  _Ixoccup_9 |   1.207186   1.068909     1.13   0.259   -.8878361    3.302208
      xpreab |  -.2990878   .2964256    -1.01   0.313   -.8800714    .2818958
       xuri1 |  -.0609462    .286367    -0.21   0.831   -.6222151    .5003228
  _Idurgrp_2 |   .6834427   .4822077     1.42   0.156   -.2616672    1.628552
  _Idurgrp_3 |   1.481166   .4099627     3.61   0.000    .6776535    2.284678
  _Idurgrp_4 |   .8638829   .4069985     2.12   0.034    .0661804    1.661585
       xhxdx |  -.3542509   .3994781    -0.89   0.375   -1.137214    .4287117
  _Iseason_2 |   .1538368   .2989305     0.51   0.607   -.4320562    .7397297
  _Iseason_3 |   .0011961   .3888124     0.00   0.998   -.7608623    .7632544
  _Iseason_4 |   .0637964    .366671     0.17   0.862   -.6548654    .7824583
       _cons |  -1.114068   .6320335    -1.76   0.078   -2.352831     .124695
------------------------------------------------------------------------------
(cat1==No Effusion is the base outcome)

.
. testparm _Icat1p*

 ( 1)  [R Effusion]_Icat1p_2 = 0
 ( 2)  [L Effusion]_Icat1p_2 = 0
 ( 3)  [Bilateral]_Icat1p_2 = 0
 ( 4)  [Missing]_Icat1p_2 = 0
 ( 5)  [R Effusion]_Icat1p_3 = 0
 ( 6)  [L Effusion]_Icat1p_3 = 0
 ( 7)  [Bilateral]_Icat1p_3 = 0
 ( 8)  [Missing]_Icat1p_3 = 0

           chi2(  8) =  335.85
         Prob > chi2 =    0.0000

. testparm _Istudy*

 ( 1)  [R Effusion]_Istudy_2 = 0
 ( 2)  [L Effusion]_Istudy_2 = 0
 ( 3)  [Bilateral]_Istudy_2 = 0
 ( 4)  [Missing]_Istudy_2 = 0
 ( 5)  [R Effusion]_Istudy_3 = 0
 ( 6)  [L Effusion]_Istudy_3 = 0
 ( 7)  [Bilateral]_Istudy_3 = 0
 ( 8)  [Missing]_Istudy_3 = 0

           chi2(  8) =    4.46
```

```
        Prob > chi2 =    0.8130

. testparm _Itrt*

 ( 1)  [R Effusion]_Itrt_1 = 0
 ( 2)  [L Effusion]_Itrt_1 = 0
 ( 3)  [Bilateral]_Itrt_1 = 0
 ( 4)  [Missing]_Itrt_1 = 0

          chi2(  4) =   15.15
        Prob > chi2 =    0.0044

. testparm xage

 ( 1)  [R Effusion]xage = 0
 ( 2)  [L Effusion]xage = 0
 ( 3)  [Bilateral]xage = 0
 ( 4)  [Missing]xage = 0

          chi2(  4) =    2.55
        Prob > chi2 =    0.6360

. testparm gender

 ( 1)  [R Effusion]gender = 0
 ( 2)  [L Effusion]gender = 0
 ( 3)  [Bilateral]gender = 0
 ( 4)  [Missing]gender = 0

          chi2(  4) =   13.15
        Prob > chi2 =    0.0106

. testparm _Ixoccup*

 ( 1)  [R Effusion]_Ixoccup_2 = 0
 ( 2)  [L Effusion]_Ixoccup_2 = 0
 ( 3)  [Bilateral]_Ixoccup_2 = 0
 ( 4)  [Missing]_Ixoccup_2 = 0
 ( 5)  [R Effusion]_Ixoccup_3 = 0
 ( 6)  [L Effusion]_Ixoccup_3 = 0
 ( 7)  [Bilateral]_Ixoccup_3 = 0
 ( 8)  [Missing]_Ixoccup_3 = 0
 ( 9)  [R Effusion]_Ixoccup_9 = 0
 (10)  [L Effusion]_Ixoccup_9 = 0
 (11)  [Bilateral]_Ixoccup_9 = 0
 (12)  [Missing]_Ixoccup_9 = 0

          chi2( 12) =   24.21
        Prob > chi2 =    0.0190

. testparm xpreab*

 ( 1)  [R Effusion]xpreab = 0
 ( 2)  [L Effusion]xpreab = 0
 ( 3)  [Bilateral]xpreab = 0
 ( 4)  [Missing]xpreab = 0
```

```
           chi2(  4) =    3.29
         Prob > chi2 =    0.5110

. testparm xuri1

 ( 1)  [R Effusion]xuri1 = 0
 ( 2)  [L Effusion]xuri1 = 0
 ( 3)  [Bilateral]xuri1 = 0
 ( 4)  [Missing]xuri1 = 0

           chi2(  4) =    3.84
         Prob > chi2 =    0.4280

. testparm _Idurgrp*

 ( 1)  [R Effusion]_Idurgrp_2 = 0
 ( 2)  [L Effusion]_Idurgrp_2 = 0
 ( 3)  [Bilateral]_Idurgrp_2 = 0
 ( 4)  [Missing]_Idurgrp_2 = 0
 ( 5)  [R Effusion]_Idurgrp_3 = 0
 ( 6)  [L Effusion]_Idurgrp_3 = 0
 ( 7)  [Bilateral]_Idurgrp_3 = 0
 ( 8)  [Missing]_Idurgrp_3 = 0
 ( 9)  [R Effusion]_Idurgrp_4 = 0
 (10)  [L Effusion]_Idurgrp_4 = 0
 (11)  [Bilateral]_Idurgrp_4 = 0
 (12)  [Missing]_Idurgrp_4 = 0

           chi2( 12) =   30.51
         Prob > chi2 =    0.0023

. testparm xhxdx

 ( 1)  [R Effusion]xhxdx = 0
 ( 2)  [L Effusion]xhxdx = 0
 ( 3)  [Bilateral]xhxdx = 0
 ( 4)  [Missing]xhxdx = 0

           chi2(  4) =    3.02
         Prob > chi2 =    0.5537

. testparm _Iseason*

 ( 1)  [R Effusion]_Iseason_2 = 0
 ( 2)  [L Effusion]_Iseason_2 = 0
 ( 3)  [Bilateral]_Iseason_2 = 0
 ( 4)  [Missing]_Iseason_2 = 0
 ( 5)  [R Effusion]_Iseason_3 = 0
 ( 6)  [L Effusion]_Iseason_3 = 0
 ( 7)  [Bilateral]_Iseason_3 = 0
 ( 8)  [Missing]_Iseason_3 = 0
 ( 9)  [R Effusion]_Iseason_4 = 0
 (10)  [L Effusion]_Iseason_4 = 0
 (11)  [Bilateral]_Iseason_4 = 0
 (12)  [Missing]_Iseason_4 = 0

           chi2( 12) =    6.07
```

```
         Prob > chi2 =    0.9125

.
. xi: mlogit cat1 i.cat1p i.trt gender i.xoccup i.durgrp if week==2,
baseoutcome(0)
i.cat1p           _Icat1p_0-4        (naturally coded; _Icat1p_0 omitted)
i.trt             _Itrt_0-1          (naturally coded; _Itrt_0 omitted)
i.xoccup          _Ixoccup_1-9       (naturally coded; _Ixoccup_1 omitted)
i.durgrp          _Idurgrp_1-4       (naturally coded; _Idurgrp_1 omitted)

note: _Icat1p_2 dropped due to collinearity
note: _Icat1p_4 dropped due to collinearity
Iteration 0:   log likelihood = -1969.5679
Iteration 1:   log likelihood = -1733.3463
Iteration 2:   log likelihood = -1674.3622
Iteration 3:   log likelihood = -1669.2657
Iteration 4:   log likelihood = -1669.2533
Iteration 5:   log likelihood = -1669.2533

Multinomial logistic regression                   Number of obs   =       1448
                                                  LR chi2(40)     =     600.63
                                                  Prob > chi2     =     0.0000
Log likelihood = -1669.2533                       Pseudo R2       =     0.1525

------------------------------------------------------------------------------
        cat1 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
R Effusion   |
   _Icat1p_1 |   3.209223   .5044244     6.36   0.000      2.22057    4.197877
   _Icat1p_3 |   1.876855   .4897517     3.83   0.000     .9169594    2.836751
     _Itrt_1 |  -.5389933    .211031    -2.55   0.011    -.9526064   -.1253802
      gender |  -.2051607   .2111177    -0.97   0.331    -.6189439    .2086224
  _Ixoccup_2 |  -.4626786   .2837351    -1.63   0.103    -1.018789     .093432
  _Ixoccup_3 |   .1344073   .2344131     0.57   0.566    -.3250339    .5938484
  _Ixoccup_9 |   .9364645   .7446758     1.26   0.209    -.5230733    2.396002
  _Idurgrp_2 |   .7511859   .3390763     2.22   0.027     .0866085    1.415763
  _Idurgrp_3 |   1.064738   .3080126     3.46   0.001     .4610444    1.668432
  _Idurgrp_4 |    .491136   .3001896     1.64   0.102    -.0972247    1.079497
       _cons |  -2.685066   .5494036    -4.89   0.000    -3.761877   -1.608255
-------------+----------------------------------------------------------------
L Effusion   |
   _Icat1p_1 |  -2.732991   .5038685    -5.42   0.000    -3.720556   -1.745427
   _Icat1p_3 |   -1.15307   .2283029    -5.05   0.000    -1.600536   -.7056047
     _Itrt_1 |  -.7180981    .216539    -3.32   0.001    -1.142507   -.2936895
      gender |  -.3043876   .2126122    -1.43   0.152    -.7210998    .1123246
  _Ixoccup_2 |  -.2906234    .292072    -1.00   0.320    -.8630739    .2818272
  _Ixoccup_3 |   .3105628   .2388346     1.30   0.193    -.1575443    .7786699
  _Ixoccup_9 |   .9269062   .7467481     1.24   0.215    -.5366931    2.390506
  _Idurgrp_2 |   .3974794   .3415447     1.16   0.245    -.2719359    1.066895
  _Idurgrp_3 |    .523926   .3075754     1.70   0.088    -.0789108    1.126763
  _Idurgrp_4 |   .3301976   .2969062     1.11   0.266    -.2517279     .912123
       _cons |   .5509157   .3303727     1.67   0.095     -.096603    1.198434
-------------+----------------------------------------------------------------
Bilateral    |
   _Icat1p_1 |  -.0856942   .3197428    -0.27   0.789    -.7123785    .5409901
   _Icat1p_3 |    1.84193   .2342932     7.86   0.000     1.382724    2.301137
     _Itrt_1 |  -.9233898   .1580113    -5.84   0.000    -1.233086   -.6136933
```

```
      gender |  -.0354319   .1602126    -0.22   0.825   -.3494428    .2785791
  _Ixoccup_2 |  -.0263115   .2009141    -0.13   0.896   -.4200958    .3674729
  _Ixoccup_3 |   .1669297    .180977     0.92   0.356   -.1877786    .5216381
  _Ixoccup_9 |   .5900157    .677356     0.87   0.384   -.7375777    1.917609
  _Idurgrp_2 |   .4765016   .2595987     1.84   0.066   -.0323025    .9853056
  _Idurgrp_3 |   .9833777    .227147     4.33   0.000    .5381779    1.428578
  _Idurgrp_4 |   .5013901    .216711     2.31   0.021    .0766443    .9261358
       _cons |  -.5793969   .3013995    -1.92   0.055   -1.170129    .0113352
-------------+----------------------------------------------------------------
Missing      |
   _Icat1p_1 |  -.0654157   .3806498    -0.17   0.864   -.8114756    .6806443
   _Icat1p_3 |  -.0674927   .3003521    -0.22   0.822    -.656172    .5211865
     _Itrt_1 |  -.8073753   .2467513    -3.27   0.001   -1.290999   -.3237516
      gender |  -.7267657   .2374155    -3.06   0.002   -1.192091   -.2614399
  _Ixoccup_2 |   .7390479   .3293024     2.24   0.025    .0936271    1.384469
  _Ixoccup_3 |   1.139851   .2922156     3.90   0.000    .5671193    1.712583
  _Ixoccup_9 |   1.312396   .8628383     1.52   0.128   -.3787361    3.003528
  _Idurgrp_2 |   .5352739   .4527959     1.18   0.237   -.3521898    1.422738
  _Idurgrp_3 |   1.424968   .3806664     3.74   0.000    .6788761    2.171061
  _Idurgrp_4 |   .9298691   .3746815     2.48   0.013    .1955069    1.664231
       _cons |  -1.617493   .4559075    -3.55   0.000   -2.511056   -.7239312
------------------------------------------------------------------------------
(cat1==No Effusion is the base outcome)

.
. testparm _Icat1p*

 ( 1)  [R Effusion]_Icat1p_1 = 0
 ( 2)  [L Effusion]_Icat1p_1 = 0
 ( 3)  [Bilateral]_Icat1p_1 = 0
 ( 4)  [Missing]_Icat1p_1 = 0
 ( 5)  [R Effusion]_Icat1p_3 = 0
 ( 6)  [L Effusion]_Icat1p_3 = 0
 ( 7)  [Bilateral]_Icat1p_3 = 0
 ( 8)  [Missing]_Icat1p_3 = 0

           chi2(  8) =  396.12
         Prob > chi2 =    0.0000

. testparm _Itrt*

 ( 1)  [R Effusion]_Itrt_1 = 0
 ( 2)  [L Effusion]_Itrt_1 = 0
 ( 3)  [Bilateral]_Itrt_1 = 0
 ( 4)  [Missing]_Itrt_1 = 0

           chi2(  4) =   35.45
         Prob > chi2 =    0.0000

. testparm gender

 ( 1)  [R Effusion]gender = 0
 ( 2)  [L Effusion]gender = 0
 ( 3)  [Bilateral]gender = 0
 ( 4)  [Missing]gender = 0

           chi2(  4) =   12.60
```

```
         Prob > chi2 =    0.0134

. testparm _Ixoccup*

 ( 1)  [R Effusion]_Ixoccup_2 = 0
 ( 2)  [L Effusion]_Ixoccup_2 = 0
 ( 3)  [Bilateral]_Ixoccup_2 = 0
 ( 4)  [Missing]_Ixoccup_2 = 0
 ( 5)  [R Effusion]_Ixoccup_3 = 0
 ( 6)  [L Effusion]_Ixoccup_3 = 0
 ( 7)  [Bilateral]_Ixoccup_3 = 0
 ( 8)  [Missing]_Ixoccup_3 = 0
 ( 9)  [R Effusion]_Ixoccup_9 = 0
 (10)  [L Effusion]_Ixoccup_9 = 0
 (11)  [Bilateral]_Ixoccup_9 = 0
 (12)  [Missing]_Ixoccup_9 = 0

           chi2( 12) =   25.20
         Prob > chi2 =    0.0139

. testparm _Idurgrp*

 ( 1)  [R Effusion]_Idurgrp_2 = 0
 ( 2)  [L Effusion]_Idurgrp_2 = 0
 ( 3)  [Bilateral]_Idurgrp_2 = 0
 ( 4)  [Missing]_Idurgrp_2 = 0
 ( 5)  [R Effusion]_Idurgrp_3 = 0
 ( 6)  [L Effusion]_Idurgrp_3 = 0
 ( 7)  [Bilateral]_Idurgrp_3 = 0
 ( 8)  [Missing]_Idurgrp_3 = 0
 ( 9)  [R Effusion]_Idurgrp_4 = 0
 (10)  [L Effusion]_Idurgrp_4 = 0
 (11)  [Bilateral]_Idurgrp_4 = 0
 (12)  [Missing]_Idurgrp_4 = 0

           chi2( 12) =   29.95
         Prob > chi2 =    0.0028

.
. * 2-4 week regression
.
. xi: mlogit cat1 i.cat1p i.study i.trt xage gender i.xoccup xpreab xuri1
i.durgrp xhxdx i.season ///
> if week==4, baseoutcome(0)
i.cat1p           _Icat1p_0-4         (naturally coded; _Icat1p_0 omitted)
i.study           _Istudy_1-3         (naturally coded; _Istudy_1 omitted)
i.trt             _Itrt_0-1           (naturally coded; _Itrt_0 omitted)
i.xoccup          _Ixoccup_1-9        (naturally coded; _Ixoccup_1 omitted)
i.durgrp          _Idurgrp_1-4        (naturally coded; _Idurgrp_1 omitted)
i.season          _Iseason_1-4        (naturally coded; _Iseason_1 omitted)

Iteration 0:   log likelihood = -1814.5434
Iteration 1:   log likelihood = -1500.9165
Iteration 2:   log likelihood = -1421.1014
Iteration 3:   log likelihood = -1369.3757
Iteration 4:   log likelihood = -1345.2005
Iteration 5:   log likelihood = -1343.7113
```

```
Iteration 6:   log likelihood = -1343.4929
Iteration 7:   log likelihood = -1343.4813
Iteration 8:   log likelihood = -1343.4812
Iteration 9:   log likelihood = -1343.4812

Multinomial logistic regression                   Number of obs   =       1286
                                                  LR chi2(84)     =     942.12
                                                  Prob > chi2     =     0.0000
Log likelihood = -1343.4812                       Pseudo R2       =     0.2596

------------------------------------------------------------------------------
        cat1 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
R Effusion   |
   _Icat1p_1 |   2.288146   .3112502     7.35   0.000     1.678106    2.898185
   _Icat1p_2 |  -.1498757   .5395384    -0.28   0.781    -1.207351    .9076002
   _Icat1p_3 |   1.550533   .3162887     4.90   0.000     .9306185    2.170447
   _Icat1p_4 |    .987764   .7397527     1.34   0.182    -.4621248    2.437653
   _Istudy_2 |   .3225392   .3248918     0.99   0.321    -.3142371    .9593154
   _Istudy_3 |  -.7357696   .3608922    -2.04   0.041    -1.443105    -.028434
     _Itrt_1 |  -.5159671   .3047631    -1.69   0.090    -1.113292    .0813577
        xage |  -.2899996   .2481513    -1.17   0.243    -.7763673    .1963681
      gender |   -.057505   .2305678    -0.25   0.803    -.5094096    .3943996
  _Ixoccup_2 |  -.1979239    .304281    -0.65   0.515    -.7943037     .398456
  _Ixoccup_3 |  -.1369444   .2518787    -0.54   0.587    -.6306177    .3567288
  _Ixoccup_9 |  -1.315533   1.180781    -1.11   0.265    -3.629822    .9987563
      xpreab |   .1587111   .2629193     0.60   0.546    -.3566013    .6740234
       xuri1 |  -.1328421   .2531992    -0.52   0.600    -.6291035    .3634193
  _Idurgrp_2 |   .0620224   .3632875     0.17   0.864     -.650008    .7740528
  _Idurgrp_3 |   .2724687    .337183     0.81   0.419    -.3883978    .9333352
  _Idurgrp_4 |  -.1878812   .3419935    -0.55   0.583    -.8581761    .4824138
       xhxdx |    -.14192    .344351    -0.41   0.680    -.8168355    .5329955
  _Iseason_2 |   .0132177   .2685544     0.05   0.961    -.5131392    .5395745
  _Iseason_3 |  -.2884107   .3323442    -0.87   0.385    -.9397935     .362972
  _Iseason_4 |  -.1311436   .3335596    -0.39   0.694    -.7849084    .5226213
       _cons |  -1.366333   .5194085    -2.63   0.009    -2.384355   -.3483112
-------------+----------------------------------------------------------------
L Effusion   |
   _Icat1p_1 |  -.0397517   .4459431    -0.09   0.929    -.9137841    .8342806
   _Icat1p_2 |   2.332793    .316346     7.37   0.000     1.712766     2.95282
   _Icat1p_3 |   1.745633   .2926938     5.96   0.000     1.171963    2.319302
   _Icat1p_4 |  -.1502465   1.098755    -0.14   0.891    -2.303767    2.003274
   _Istudy_2 |   .7214573   .3363497     2.14   0.032     .0622239    1.380691
   _Istudy_3 |   .4800981   .3318384     1.45   0.148    -.1702931    1.130489
     _Itrt_1 |  -.1436574   .2809098    -0.51   0.609    -.6942306    .4069157
        xage |  -.0103309   .2407784    -0.04   0.966    -.4822479     .461586
      gender |   .0338294   .2274263     0.15   0.882    -.4119181    .4795768
  _Ixoccup_2 |  -.6262258   .3064443    -2.04   0.041    -1.226846   -.0256061
  _Ixoccup_3 |  -.2698547   .2454375    -1.10   0.272    -.7509034     .211194
  _Ixoccup_9 |   .0738135   .9919642     0.07   0.941    -1.870401    2.018028
      xpreab |   .3309318   .2635978     1.26   0.209    -.1857103    .8475739
       xuri1 |  -.0415228   .2565192    -0.16   0.871    -.5442913    .4612456
  _Idurgrp_2 |  -.7128329   .3923623    -1.82   0.069    -1.481849    .0561832
  _Idurgrp_3 |   .4875304   .3199054     1.52   0.128    -.1394726    1.114533
  _Idurgrp_4 |  -.0658253   .3274445    -0.20   0.841    -.7076047    .5759541
       xhxdx |    .510912   .4281914     1.19   0.233    -.3283276    1.350152
  _Iseason_2 |  -.1106914   .2659062    -0.42   0.677     -.631858    .4104753
```

```
   _Iseason_3 |  -.3062549   .3262167    -0.94   0.348   -.9456279    .3331182
   _Iseason_4 |  -.0116153   .3301493    -0.04   0.972    -.658696    .6354653
        _cons |   -2.58981   .5837273    -4.44   0.000   -3.733895   -1.445726
-------------+----------------------------------------------------------------
Bilateral    |
    _Icat1p_1 |   1.047359   .2928496     3.58   0.000     .473384    1.621333
    _Icat1p_2 |    1.40061   .3032023     4.62   0.000     .806344    1.994875
    _Icat1p_3 |   3.280354   .2356332    13.92   0.000    2.818521    3.742186
    _Icat1p_4 |   1.920825   .5115963     3.75   0.000    .9181145    2.923535
    _Istudy_2 |   .6497764   .2588621     2.51   0.012    .1424159    1.157137
    _Istudy_3 |   .4029986   .2562192     1.57   0.116   -.0991817    .9051789
       _Itrt_1 |  -.4774405   .2258545    -2.11   0.035   -.9201073   -.0347737
          xage |   .1117674   .1881827     0.59   0.553   -.2570638    .4805986
        gender |  -.3372479   .1761128    -1.91   0.055   -.6824225    .0079268
   _Ixoccup_2 |  -.0894852   .2276562    -0.39   0.694   -.5356831    .3567126
   _Ixoccup_3 |  -.0062195   .1975066    -0.03   0.975   -.3933254    .3808864
   _Ixoccup_9 |  -.7423434   .8800361    -0.84   0.399   -2.467183    .9824957
        xpreab |  -.0025114   .2025971    -0.01   0.990   -.3995944    .3945717
         xuri1 |   .0249182   .1939424     0.13   0.898   -.3552019    .4050383
   _Idurgrp_2 |  -.2176496   .2937891    -0.74   0.459   -.7934655    .3581664
   _Idurgrp_3 |   .5468629   .2621033     2.09   0.037    .0331499    1.060576
   _Idurgrp_4 |   .1415532   .2570176     0.55   0.582   -.3621919    .6452984
         xhxdx |   .0393669   .2763091     0.14   0.887   -.5021889    .5809227
   _Iseason_2 |  -.4765435   .2077472    -2.29   0.022   -.8837205   -.0693664
   _Iseason_3 |  -1.094269   .2702837    -4.05   0.000   -1.624015   -.5645222
   _Iseason_4 |   .0336318   .2471475     0.14   0.892   -.4507684     .518032
        _cons |   -1.22861   .4169334    -2.95   0.003   -2.045784   -.4114351
-------------+----------------------------------------------------------------
Missing      |
    _Icat1p_1 |   .6660998   .5782874     1.15   0.249   -.4673227    1.799522
    _Icat1p_2 |   .9360831   .5870627     1.59   0.111   -.2145387    2.086705
    _Icat1p_3 |   1.598806   .4657563     3.43   0.001    .6859404    2.511671
    _Icat1p_4 |   5.298002   .5637875     9.40   0.000    4.192998    6.403005
    _Istudy_2 |  -.0442759   .4497384    -0.10   0.922    -.925747    .8371952
    _Istudy_3 |  -.1163372   .4700364    -0.25   0.805   -1.037592    .8049172
       _Itrt_1 |   -.063007   .4065763    -0.15   0.877   -.8598818    .7338679
          xage |   .4354618   .3234858     1.35   0.178   -.1985588    1.069482
        gender |  -.7439679   .3024459    -2.46   0.014   -1.336751   -.1511848
   _Ixoccup_2 |   -.615647   .4169964    -1.48   0.140   -1.432945     .201651
   _Ixoccup_3 |  -.3661642    .356141    -1.03   0.304   -1.064188    .3318593
   _Ixoccup_9 |  -.6209991   1.311372    -0.47   0.636   -3.191241    1.949242
        xpreab |   -.835165   .3588664    -2.33   0.020    -1.53853   -.1317997
         xuri1 |    .132896   .3423436     0.39   0.698    -.538085    .8038771
   _Idurgrp_2 |  -.1085202   .5348923    -0.20   0.839    -1.15689    .9398494
   _Idurgrp_3 |   .2593767    .467594     0.55   0.579   -.6570906    1.175844
   _Idurgrp_4 |  -.2359329   .4634232    -0.51   0.611   -1.144226    .6723598
         xhxdx |  -.1698088   .4406823    -0.39   0.700    -1.03353    .6939126
   _Iseason_2 |   -.223143   .3705197    -0.60   0.547   -.9493483    .5030623
   _Iseason_3 |  -.2110105   .4507144    -0.47   0.640   -1.094394    .6723735
   _Iseason_4 |   .0995606   .4338464     0.23   0.818   -.7507626    .9498839
        _cons |  -1.550166   .6998451    -2.22   0.027   -2.921837   -.1784945
------------------------------------------------------------------------------
(cat1==No Effusion is the base outcome)

.
. testparm _Icat1p*
```

```
 ( 1)  [R Effusion]_Icat1p_1 = 0
 ( 2)  [L Effusion]_Icat1p_1 = 0
 ( 3)  [Bilateral]_Icat1p_1 = 0
 ( 4)  [Missing]_Icat1p_1 = 0
 ( 5)  [R Effusion]_Icat1p_2 = 0
 ( 6)  [L Effusion]_Icat1p_2 = 0
 ( 7)  [Bilateral]_Icat1p_2 = 0
 ( 8)  [Missing]_Icat1p_2 = 0
 ( 9)  [R Effusion]_Icat1p_3 = 0
 (10)  [L Effusion]_Icat1p_3 = 0
 (11)  [Bilateral]_Icat1p_3 = 0
 (12)  [Missing]_Icat1p_3 = 0
 (13)  [R Effusion]_Icat1p_4 = 0
 (14)  [L Effusion]_Icat1p_4 = 0
 (15)  [Bilateral]_Icat1p_4 = 0
 (16)  [Missing]_Icat1p_4 = 0

           chi2( 16) =  668.34
         Prob > chi2 =    0.0000

. testparm _Istudy*

 ( 1)  [R Effusion]_Istudy_2 = 0
 ( 2)  [L Effusion]_Istudy_2 = 0
 ( 3)  [Bilateral]_Istudy_2 = 0
 ( 4)  [Missing]_Istudy_2 = 0
 ( 5)  [R Effusion]_Istudy_3 = 0
 ( 6)  [L Effusion]_Istudy_3 = 0
 ( 7)  [Bilateral]_Istudy_3 = 0
 ( 8)  [Missing]_Istudy_3 = 0

           chi2(  8) =   20.27
         Prob > chi2 =    0.0094

. testparm _Itrt*

 ( 1)  [R Effusion]_Itrt_1 = 0
 ( 2)  [L Effusion]_Itrt_1 = 0
 ( 3)  [Bilateral]_Itrt_1 = 0
 ( 4)  [Missing]_Itrt_1 = 0

           chi2(  4) =    6.30
         Prob > chi2 =    0.1779

. testparm xage

 ( 1)  [R Effusion]xage = 0
 ( 2)  [L Effusion]xage = 0
 ( 3)  [Bilateral]xage = 0
 ( 4)  [Missing]xage = 0

           chi2(  4) =    4.82
         Prob > chi2 =    0.3064

. testparm gender

 ( 1)  [R Effusion]gender = 0
```

```
 ( 2)  [L Effusion]gender = 0
 ( 3)  [Bilateral]gender = 0
 ( 4)  [Missing]gender = 0

           chi2(  4) =    9.67
         Prob > chi2 =    0.0463

. testparm _Ixoccup*

 ( 1)  [R Effusion]_Ixoccup_2 = 0
 ( 2)  [L Effusion]_Ixoccup_2 = 0
 ( 3)  [Bilateral]_Ixoccup_2 = 0
 ( 4)  [Missing]_Ixoccup_2 = 0
 ( 5)  [R Effusion]_Ixoccup_3 = 0
 ( 6)  [L Effusion]_Ixoccup_3 = 0
 ( 7)  [Bilateral]_Ixoccup_3 = 0
 ( 8)  [Missing]_Ixoccup_3 = 0
 ( 9)  [R Effusion]_Ixoccup_9 = 0
 (10)  [L Effusion]_Ixoccup_9 = 0
 (11)  [Bilateral]_Ixoccup_9 = 0
 (12)  [Missing]_Ixoccup_9 = 0

           chi2( 12) =    8.87
         Prob > chi2 =    0.7140

. testparm xpreab*

 ( 1)  [R Effusion]xpreab = 0
 ( 2)  [L Effusion]xpreab = 0
 ( 3)  [Bilateral]xpreab = 0
 ( 4)  [Missing]xpreab = 0

           chi2(  4) =    9.41
         Prob > chi2 =    0.0516

. testparm xuri1

 ( 1)  [R Effusion]xuri1 = 0
 ( 2)  [L Effusion]xuri1 = 0
 ( 3)  [Bilateral]xuri1 = 0
 ( 4)  [Missing]xuri1 = 0

           chi2(  4) =    0.68
         Prob > chi2 =    0.9536

. testparm _Idurgrp*

 ( 1)  [R Effusion]_Idurgrp_2 = 0
 ( 2)  [L Effusion]_Idurgrp_2 = 0
 ( 3)  [Bilateral]_Idurgrp_2 = 0
 ( 4)  [Missing]_Idurgrp_2 = 0
 ( 5)  [R Effusion]_Idurgrp_3 = 0
 ( 6)  [L Effusion]_Idurgrp_3 = 0
 ( 7)  [Bilateral]_Idurgrp_3 = 0
 ( 8)  [Missing]_Idurgrp_3 = 0
 ( 9)  [R Effusion]_Idurgrp_4 = 0
 (10)  [L Effusion]_Idurgrp_4 = 0
```

```
 (11)  [Bilateral]_Idurgrp_4 = 0
 (12)  [Missing]_Idurgrp_4 = 0

           chi2( 12) =   18.36
         Prob > chi2 =    0.1053

. testparm xhxdx

 ( 1)  [R Effusion]xhxdx = 0
 ( 2)  [L Effusion]xhxdx = 0
 ( 3)  [Bilateral]xhxdx = 0
 ( 4)  [Missing]xhxdx = 0

           chi2(  4) =    2.26
         Prob > chi2 =    0.6873

. testparm _Iseason*

 ( 1)  [R Effusion]_Iseason_2 = 0
 ( 2)  [L Effusion]_Iseason_2 = 0
 ( 3)  [Bilateral]_Iseason_2 = 0
 ( 4)  [Missing]_Iseason_2 = 0
 ( 5)  [R Effusion]_Iseason_3 = 0
 ( 6)  [L Effusion]_Iseason_3 = 0
 ( 7)  [Bilateral]_Iseason_3 = 0
 ( 8)  [Missing]_Iseason_3 = 0
 ( 9)  [R Effusion]_Iseason_4 = 0
 (10)  [L Effusion]_Iseason_4 = 0
 (11)  [Bilateral]_Iseason_4 = 0
 (12)  [Missing]_Iseason_4 = 0

           chi2( 12) =   25.02
         Prob > chi2 =    0.0147

.
. xi: mlogit cat1 i.cat1p i.study i.trt gender xpreab i.durgrp i.season ///
> if week==4, baseoutcome(0)
i.cat1p           _Icat1p_0-4         (naturally coded; _Icat1p_0 omitted)
i.study           _Istudy_1-3         (naturally coded; _Istudy_1 omitted)
i.trt             _Itrt_0-1           (naturally coded; _Itrt_0 omitted)
i.durgrp          _Idurgrp_1-4        (naturally coded; _Idurgrp_1 omitted)
i.season          _Iseason_1-4        (naturally coded; _Iseason_1 omitted)

Iteration 0:   log likelihood = -2033.5652
Iteration 1:   log likelihood = -1689.4859
Iteration 2:   log likelihood = -1592.7834
Iteration 3:   log likelihood = -1548.6245
Iteration 4:   log likelihood = -1518.9505
Iteration 5:   log likelihood = -1515.0547
Iteration 6:   log likelihood = -1514.2083
Iteration 7:   log likelihood =    -1514.1
Iteration 8:   log likelihood = -1514.0966
Iteration 9:   log likelihood = -1514.0966

Multinomial logistic regression                   Number of obs   =       1447
                                                  LR chi2(60)     =    1038.94
                                                  Prob > chi2     =     0.0000
```

Log likelihood = -1514.0966 Pseudo R2 = 0.2554

cat1	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
R Effusion						
_Icat1p_1	2.349943	.2990258	7.86	0.000	1.763863	2.936022
_Icat1p_2	-.0332155	.4985454	-0.07	0.947	-1.010347	.9439156
_Icat1p_3	1.561644	.3031183	5.15	0.000	.9675426	2.155744
_Icat1p_4	1.026793	.7333825	1.40	0.161	-.4106103	2.464196
_Istudy_2	.4078761	.3127889	1.30	0.192	-.2051789	1.020931
_Istudy_3	-.6185018	.3458133	-1.79	0.074	-1.296283	.0592799
_Itrt_1	-.4894066	.3019528	-1.62	0.105	-1.081223	.1024101
gender	-.0678529	.2175112	-0.31	0.755	-.494167	.3584612
xpreab	.1305204	.2418819	0.54	0.589	-.3435595	.6046003
_Idurgrp_2	.1194865	.3391043	0.35	0.725	-.5451457	.7841187
_Idurgrp_3	.2066771	.3170785	0.65	0.515	-.4147854	.8281397
_Idurgrp_4	-.0711004	.3242195	-0.22	0.826	-.706559	.5643583
_Iseason_2	.0212802	.2604504	0.08	0.935	-.4891933	.5317536
_Iseason_3	-.2044459	.3172216	-0.64	0.519	-.8261889	.4172971
_Iseason_4	-.2125607	.3029517	-0.70	0.483	-.8063351	.3812136
_cons	-1.860587	.430654	-4.32	0.000	-2.704653	-1.01652
L Effusion						
_Icat1p_1	-.187028	.4345216	-0.43	0.667	-1.038675	.6646187
_Icat1p_2	2.258533	.2898187	7.79	0.000	1.690499	2.826567
_Icat1p_3	1.638277	.2711368	6.04	0.000	1.106859	2.169696
_Icat1p_4	-.3162962	1.0923	-0.29	0.772	-2.457165	1.824572
_Istudy_2	.5692573	.310547	1.83	0.067	-.0394037	1.177918
_Istudy_3	.3156129	.3028151	1.04	0.297	-.2778938	.9091195
_Itrt_1	-.1140144	.276054	-0.41	0.680	-.6550702	.4270414
gender	.0567206	.2100062	0.27	0.787	-.354884	.4683253
xpreab	.3481582	.23551	1.48	0.139	-.113433	.8097493
_Idurgrp_2	-.5483059	.3557557	-1.54	0.123	-1.245574	.1489625
_Idurgrp_3	.5171038	.2925971	1.77	0.077	-.0563761	1.090584
_Idurgrp_4	-.0168018	.3001382	-0.06	0.955	-.6050618	.5714583
_Iseason_2	-.1207573	.2509226	-0.48	0.630	-.6125565	.371042
_Iseason_3	-.2360193	.3020982	-0.78	0.435	-.8281209	.3560823
_Iseason_4	-.0981538	.2914014	-0.34	0.736	-.6692901	.4729825
_cons	-2.221479	.4187749	-5.30	0.000	-3.042263	-1.400695
Bilateral						
_Icat1p_1	1.170552	.279826	4.18	0.000	.6221028	1.719001
_Icat1p_2	1.423294	.2879054	4.94	0.000	.85901	1.987579
_Icat1p_3	3.338708	.2270463	14.70	0.000	2.893705	3.78371
_Icat1p_4	1.967681	.5058517	3.89	0.000	.9762296	2.959132
_Istudy_2	.6058366	.2451726	2.47	0.013	.1253071	1.086366
_Istudy_3	.3500485	.2400893	1.46	0.145	-.120518	.8206149
_Itrt_1	-.4679239	.2235191	-2.09	0.036	-.9060132	-.0298345
gender	-.3196497	.1648646	-1.94	0.053	-.6427785	.0034791
xpreab	-.0585738	.18258	-0.32	0.748	-.416424	.2992764
_Idurgrp_2	-.1055591	.2720952	-0.39	0.698	-.6388558	.4277376
_Idurgrp_3	.5112517	.2430423	2.10	0.035	.0348976	.9876058
_Idurgrp_4	.1528332	.2417044	0.63	0.527	-.3208988	.6265652
_Iseason_2	-.4803751	.2002225	-2.40	0.016	-.872804	-.0879462
_Iseason_3	-.9748663	.2538136	-3.84	0.000	-1.472332	-.4774007
_Iseason_4	-.0917672	.2224969	-0.41	0.680	-.5278532	.3443188

```
       _cons |  -1.192402   .3317557    -3.59   0.000   -1.842631   -.5421725
-------------+----------------------------------------------------------------
Missing      |
   _Icat1p_1 |   .5983444   .5577694     1.07   0.283   -.4948636    1.691552
   _Icat1p_2 |    .940097   .5417407     1.74   0.083   -.1216953    2.001889
   _Icat1p_3 |   1.456276   .4393617     3.31   0.001     .595143    2.317409
   _Icat1p_4 |   5.272293    .533648     9.88   0.000    4.226363    6.318224
   _Istudy_2 |   -.119238   .4301379    -0.28   0.782   -.9622928    .7238168
   _Istudy_3 |  -.2719842    .449607    -0.60   0.545   -1.153198    .6092293
     _Itrt_1 |  -.0821821   .4085096    -0.20   0.841   -.8828462     .718482
      gender |  -.6177598   .2870602    -2.15   0.031   -1.180387   -.0551322
      xpreab |  -.6239173   .3227849    -1.93   0.053   -1.256564    .0087295
  _Idurgrp_2 |  -.3608199   .5077002    -0.71   0.477   -1.355894    .6342541
  _Idurgrp_3 |   .0809435   .4320736     0.19   0.851   -.7659052    .9277923
  _Idurgrp_4 |  -.2591885   .4373931    -0.59   0.553   -1.116463    .5980863
  _Iseason_2 |  -.2341736   .3589195    -0.65   0.514    -.937643    .4692957
  _Iseason_3 |  -.2979656   .4332548    -0.69   0.492   -1.147129    .5511983
  _Iseason_4 |  -.1104768   .3993371    -0.28   0.782   -.8931632    .6722095
       _cons |  -1.710224   .5685727    -3.01   0.003   -2.824606   -.5958422
------------------------------------------------------------------------------
(cat1==No Effusion is the base outcome)

.
. testparm _Icat1p*

 ( 1)  [R Effusion]_Icat1p_1 = 0
 ( 2)  [L Effusion]_Icat1p_1 = 0
 ( 3)  [Bilateral]_Icat1p_1 = 0
 ( 4)  [Missing]_Icat1p_1 = 0
 ( 5)  [R Effusion]_Icat1p_2 = 0
 ( 6)  [L Effusion]_Icat1p_2 = 0
 ( 7)  [Bilateral]_Icat1p_2 = 0
 ( 8)  [Missing]_Icat1p_2 = 0
 ( 9)  [R Effusion]_Icat1p_3 = 0
 (10)  [L Effusion]_Icat1p_3 = 0
 (11)  [Bilateral]_Icat1p_3 = 0
 (12)  [Missing]_Icat1p_3 = 0
 (13)  [R Effusion]_Icat1p_4 = 0
 (14)  [L Effusion]_Icat1p_4 = 0
 (15)  [Bilateral]_Icat1p_4 = 0
 (16)  [Missing]_Icat1p_4 = 0

           chi2( 16) =  783.60
         Prob > chi2 =    0.0000

. testparm _Istudy*

 ( 1)  [R Effusion]_Istudy_2 = 0
 ( 2)  [L Effusion]_Istudy_2 = 0
 ( 3)  [Bilateral]_Istudy_2 = 0
 ( 4)  [Missing]_Istudy_2 = 0
 ( 5)  [R Effusion]_Istudy_3 = 0
 ( 6)  [L Effusion]_Istudy_3 = 0
 ( 7)  [Bilateral]_Istudy_3 = 0
 ( 8)  [Missing]_Istudy_3 = 0

           chi2(  8) =   18.57
```

```
         Prob > chi2 =    0.0173

. testparm _Itrt*

 ( 1)  [R Effusion]_Itrt_1 = 0
 ( 2)  [L Effusion]_Itrt_1 = 0
 ( 3)  [Bilateral]_Itrt_1 = 0
 ( 4)  [Missing]_Itrt_1 = 0

           chi2(  4) =    6.10
         Prob > chi2 =    0.1921

. testparm gender

 ( 1)  [R Effusion]gender = 0
 ( 2)  [L Effusion]gender = 0
 ( 3)  [Bilateral]gender = 0
 ( 4)  [Missing]gender = 0

           chi2(  4) =    8.87
         Prob > chi2 =    0.0645

. testparm xpreab*

 ( 1)  [R Effusion]xpreab = 0
 ( 2)  [L Effusion]xpreab = 0
 ( 3)  [Bilateral]xpreab = 0
 ( 4)  [Missing]xpreab = 0

           chi2(  4) =    8.54
         Prob > chi2 =    0.0737

. testparm _Idurgrp*

 ( 1)  [R Effusion]_Idurgrp_2 = 0
 ( 2)  [L Effusion]_Idurgrp_2 = 0
 ( 3)  [Bilateral]_Idurgrp_2 = 0
 ( 4)  [Missing]_Idurgrp_2 = 0
 ( 5)  [R Effusion]_Idurgrp_3 = 0
 ( 6)  [L Effusion]_Idurgrp_3 = 0
 ( 7)  [Bilateral]_Idurgrp_3 = 0
 ( 8)  [Missing]_Idurgrp_3 = 0
 ( 9)  [R Effusion]_Idurgrp_4 = 0
 (10)  [L Effusion]_Idurgrp_4 = 0
 (11)  [Bilateral]_Idurgrp_4 = 0
 (12)  [Missing]_Idurgrp_4 = 0

           chi2( 12) =   17.01
         Prob > chi2 =    0.1491

. testparm _Iseason*

 ( 1)  [R Effusion]_Iseason_2 = 0
 ( 2)  [L Effusion]_Iseason_2 = 0
 ( 3)  [Bilateral]_Iseason_2 = 0
 ( 4)  [Missing]_Iseason_2 = 0
 ( 5)  [R Effusion]_Iseason_3 = 0
```

```
 ( 6)  [L Effusion]_Iseason_3 = 0
 ( 7)  [Bilateral]_Iseason_3 = 0
 ( 8)  [Missing]_Iseason_3 = 0
 ( 9)  [R Effusion]_Iseason_4 = 0
 (10)  [L Effusion]_Iseason_4 = 0
 (11)  [Bilateral]_Iseason_4 = 0
 (12)  [Missing]_Iseason_4 = 0

           chi2( 12) =   23.30
         Prob > chi2 =    0.0253

.xi: mlogit cat1 i.cat1p i.study xage gender xpreab i.durgrp i.season ///
> if week==4, baseoutcome(0)
i.cat1p           _Icat1p_0-4         (naturally coded; _Icat1p_0 omitted)
i.study           _Istudy_1-3         (naturally coded; _Istudy_1 omitted)
i.durgrp          _Idurgrp_1-4        (naturally coded; _Idurgrp_1 omitted)
i.season          _Iseason_1-4        (naturally coded; _Iseason_1 omitted)

Iteration 0:   log likelihood = -2033.5652
Iteration 1:   log likelihood =   -1689.74
Iteration 2:   log likelihood = -1593.1771
Iteration 3:   log likelihood = -1549.5486
Iteration 4:   log likelihood = -1519.4673
Iteration 5:   log likelihood = -1515.4733
Iteration 6:   log likelihood = -1514.6068
Iteration 7:   log likelihood = -1514.4949
Iteration 8:   log likelihood = -1514.4913
Iteration 9:   log likelihood = -1514.4913

Multinomial logistic regression                   Number of obs   =       1447
                                                  LR chi2(60)     =    1038.15
                                                  Prob > chi2     =     0.0000
Log likelihood = -1514.4913                       Pseudo R2       =     0.2553

------------------------------------------------------------------------------
        cat1 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
R Effusion   |
   _Icat1p_1 |   2.368623    .298807     7.93   0.000     1.782972    2.954274
   _Icat1p_2 |  -.0053832   .4984058    -0.01   0.991    -.9822407    .9714743
   _Icat1p_3 |   1.592778   .3024302     5.27   0.000     1.000025     2.18553
   _Icat1p_4 |   1.070592   .7325532     1.46   0.144    -.3651859     2.50637
   _Istudy_2 |   .0787384   .2348973     0.34   0.737    -.3816519    .5391287
   _Istudy_3 |  -.9005529   .3138897    -2.87   0.004    -1.515765   -.2853404
        xage |   -.301118   .2370292    -1.27   0.204    -.7656868    .1634507
      gender |  -.0539218   .2178761    -0.25   0.805    -.4809511    .3731075
      xpreab |   .1472656   .2422429     0.61   0.543    -.3275217    .6220528
  _Idurgrp_2 |   .0860492   .3389239     0.25   0.800    -.5782295    .7503279
  _Idurgrp_3 |   .1456515   .3180196     0.46   0.647    -.4776554    .7689584
  _Idurgrp_4 |  -.1480511   .3253231    -0.46   0.649    -.7856727    .4895704
  _Iseason_2 |   .0128645   .2601749     0.05   0.961    -.4970689    .5227978
  _Iseason_3 |  -.2185165   .3168047    -0.69   0.490    -.8394424    .4024094
  _Iseason_4 |  -.2190234   .3028582    -0.72   0.470    -.8126145    .3745678
       _cons |  -1.760977    .433575    -4.06   0.000    -2.610768   -.9111852
-------------+----------------------------------------------------------------
L Effusion   |
   _Icat1p_1 |  -.1864645   .4343755    -0.43   0.668    -1.037825    .6648959
```

```
   _Icat1p_2 |   2.261833   .2892583     7.82   0.000     1.694898    2.828769
   _Icat1p_3 |   1.637469   .2703773     6.06   0.000      1.10754    2.167399
   _Icat1p_4 |  -.3076539   1.092057    -0.28   0.778    -2.448046    1.832738
   _Istudy_2 |   .4883885   .2368908     2.06   0.039     .0240911     .952686
   _Istudy_3 |   .2347662   .2650381     0.89   0.376    -.2846989    .7542313
        xage |  -.1981233   .2267353    -0.87   0.382    -.6425163    .2462697
      gender |   .0552331   .2099052     0.26   0.792    -.3561735    .4666396
      xpreab |     .36658    .236305     1.55   0.121    -.0965692    .8297293
  _Idurgrp_2 |   -.575457   .3569811    -1.61   0.107    -1.275127    .1242132
  _Idurgrp_3 |   .4807646   .2945192     1.63   0.103    -.0964824    1.058012
  _Idurgrp_4 |  -.0613362   .3031316    -0.20   0.840    -.6554632    .5327907
  _Iseason_2 |  -.1032537   .2518917    -0.41   0.682    -.5969524    .3904449
  _Iseason_3 |  -.2325702   .3024779    -0.77   0.442    -.8254159    .3602756
  _Iseason_4 |  -.0938249   .2915356    -0.32   0.748    -.6652241    .4775744
       _cons |  -2.148777   .4239244    -5.07   0.000    -2.979653     -1.3179
-------------+----------------------------------------------------------------
Bilateral    |
   _Icat1p_1 |   1.193787   .2791339     4.28   0.000     .6466941    1.740879
   _Icat1p_2 |   1.449235   .2877659     5.04   0.000     .8852247    2.013246
   _Icat1p_3 |   3.378048   .2267198    14.90   0.000     2.933686    3.822411
   _Icat1p_4 |   2.021219   .5042094     4.01   0.000     1.032987    3.009451
   _Istudy_2 |   .2817901   .1872478     1.50   0.132    -.0852089    .6487891
   _Istudy_3 |   .1180993   .2106875     0.56   0.575    -.2948405    .5310391
        xage |   .0874295    .177537     0.49   0.622    -.2605366    .4353955
      gender |  -.3236468   .1647806    -1.96   0.050    -.6466109   -.0006827
      xpreab |  -.0888231   .1835628    -0.48   0.628    -.4485996    .2709533
  _Idurgrp_2 |  -.1014669   .2727452    -0.37   0.710    -.6360376    .4331038
  _Idurgrp_3 |   .5190673   .2446265     2.12   0.034     .0396082    .9985264
  _Idurgrp_4 |   .1621039   .2441855     0.66   0.507    -.3164908    .6406987
  _Iseason_2 |  -.4966469   .1998848    -2.48   0.013    -.8884139   -.1048799
  _Iseason_3 |  -.9901613   .2538968    -3.90   0.000     -1.48779   -.4925328
  _Iseason_4 |  -.0872239    .222462    -0.39   0.695    -.5232415    .3487937
       _cons |  -1.229651   .3375827    -3.64   0.000    -1.891301    -.568001
-------------+----------------------------------------------------------------
Missing      |
   _Icat1p_1 |   .5919823   .5577892     1.06   0.289    -.5012645    1.685229
   _Icat1p_2 |   .9292975    .542082     1.71   0.086    -.1331636    1.991759
   _Icat1p_3 |   1.461075   .4382597     3.33   0.001     .6021019    2.320048
   _Icat1p_4 |    5.26634   .5323215     9.89   0.000     4.223009    6.309671
   _Istudy_2 |  -.2026391    .329631    -0.61   0.539    -.8487041    .4434258
   _Istudy_3 |  -.3048928   .3952816    -0.77   0.441    -1.079631    .4698449
        xage |    .295155   .3081298     0.96   0.338    -.3087683    .8990784
      gender |   -.615353   .2870371    -2.14   0.032    -1.177935   -.0527705
      xpreab |  -.6659993   .3269659    -2.04   0.042    -1.306841   -.0251579
  _Idurgrp_2 |  -.3076001   .5107884    -0.60   0.547    -1.308727    .6935267
  _Idurgrp_3 |   .1319428    .438083     0.30   0.763    -.7266841    .9905698
  _Idurgrp_4 |  -.2026095   .4429051    -0.46   0.647    -1.070688    .6654686
  _Iseason_2 |  -.2399404   .3581509    -0.67   0.503    -.9419033    .4620226
  _Iseason_3 |   -.311406   .4348247    -0.72   0.474    -1.163647    .5408348
  _Iseason_4 |  -.1132277   .4005313    -0.28   0.777    -.8982546    .6717991
       _cons |  -1.816873   .5843497    -3.11   0.002    -2.962178    -.671569
------------------------------------------------------------------------------
(cat1==No Effusion is the base outcome)

.
. testparm _Icat1p*
```

```
 ( 1)  [R Effusion]_Icat1p_1 = 0
 ( 2)  [L Effusion]_Icat1p_1 = 0
 ( 3)  [Bilateral]_Icat1p_1 = 0
 ( 4)  [Missing]_Icat1p_1 = 0
 ( 5)  [R Effusion]_Icat1p_2 = 0
 ( 6)  [L Effusion]_Icat1p_2 = 0
 ( 7)  [Bilateral]_Icat1p_2 = 0
 ( 8)  [Missing]_Icat1p_2 = 0
 ( 9)  [R Effusion]_Icat1p_3 = 0
 (10)  [L Effusion]_Icat1p_3 = 0
 (11)  [Bilateral]_Icat1p_3 = 0
 (12)  [Missing]_Icat1p_3 = 0
 (13)  [R Effusion]_Icat1p_4 = 0
 (14)  [L Effusion]_Icat1p_4 = 0
 (15)  [Bilateral]_Icat1p_4 = 0
 (16)  [Missing]_Icat1p_4 = 0

           chi2( 16) =  790.37
         Prob > chi2 =    0.0000

. testparm _Istudy*

 ( 1)  [R Effusion]_Istudy_2 = 0
 ( 2)  [L Effusion]_Istudy_2 = 0
 ( 3)  [Bilateral]_Istudy_2 = 0
 ( 4)  [Missing]_Istudy_2 = 0
 ( 5)  [R Effusion]_Istudy_3 = 0
 ( 6)  [L Effusion]_Istudy_3 = 0
 ( 7)  [Bilateral]_Istudy_3 = 0
 ( 8)  [Missing]_Istudy_3 = 0

           chi2(  8) =   18.46
         Prob > chi2 =    0.0180

. testparm gender

 ( 1)  [R Effusion]gender = 0
 ( 2)  [L Effusion]gender = 0
 ( 3)  [Bilateral]gender = 0
 ( 4)  [Missing]gender = 0

           chi2(  4) =    9.02
         Prob > chi2 =    0.0607

. testparm xpreab*

 ( 1)  [R Effusion]xpreab = 0
 ( 2)  [L Effusion]xpreab = 0
 ( 3)  [Bilateral]xpreab = 0
 ( 4)  [Missing]xpreab = 0

           chi2(  4) =    9.83
         Prob > chi2 =    0.0433

. testparm _Iseason*

 ( 1)  [R Effusion]_Iseason_2 = 0
```

```
( 2)  [L Effusion]_Iseason_2 = 0
( 3)  [Bilateral]_Iseason_2 = 0
( 4)  [Missing]_Iseason_2 = 0
( 5)  [R Effusion]_Iseason_3 = 0
( 6)  [L Effusion]_Iseason_3 = 0
( 7)  [Bilateral]_Iseason_3 = 0
( 8)  [Missing]_Iseason_3 = 0
( 9)  [R Effusion]_Iseason_4 = 0
(10)  [L Effusion]_Iseason_4 = 0
(11)  [Bilateral]_Iseason_4 = 0
(12)  [Missing]_Iseason_4 = 0

          chi2( 12) =   24.35
        Prob > chi2 =    0.0182
```

BIBLIOGRAPHY

American Academy of Family Physicians, American Academy of Otolaryngology-Head and Neck Surgery, American Academy of Pediatrics Subcommittee on Otitis Media with Effusion. Otitis media with effusion. Pediatrics 2004; 113(5):1412-1429.

Cantekin EI, Mandel EM, Bluestone CD, et al. Lack of efficacy of a decongestant-antihistamine combination for otitis media with effusion ("secretory" otitis media) in children: results of a double-blind, randomized trial. N Eng J of Med 1983; 308:297-301.

Cantekin EI. Algorithm for diagnosis of otitis media with effusion. Ann Otol Rhinol Laryngol 1983; 92:Suppl 107:6-7.

Daly KA, Hunter LL, Giebink GS. Chronic otitis media with effusion. Pediatr in Rev 1999; 20:85-94.

Damoiseaux RAMJ, Rovers MM, Van Balen FAM, Hoes AW, de Melker RA. Long-term prognosis of acute otitis media in infancy: determinants of recurrent acute otitis media and persistent middle ear effusion. Family Practice 2006; 23:40-45.

Glasziou PP, Del Mar CB, Sanders SL, Hayem M. Antibiotics for acute otitis media in children (Cochrane Review), The Cochrane Library, Update Software, Oxford 2002; Issue 2.

Huber PJ. The behavior of maximum likelihood estimates under nonstandard conditions. Proceedings of the fifth Berkeley symposium on mathematical statistics and probability. University of California Press 1967; 221-233.

Jero, J, Karma P. Prognosis of acute otitis media: factors associated with the development of recurrent acute otitis media. Acta Otolaryngol (Stockh) 1997a; Suppl 529:30-33.

Jero J, Virolainen A, Virtanen M, Eskola J, Karma P. Prognosis of acute otitis media: Factors associated with poor outcome. Acta Otolaryngol (Stockh) 1997b; 117:278-283.

Jero J, Karma P. Bacteriological findings and persistence of middle ear effusion in otitis media with effusion. Acta Otolaryngol (Stockh) 1997c; Suppl 529:22-26.

Johnson IJ, Brooks T, Hutton DA, Birchall JP, Pearson JP. Compositional differences between bilateral middle ear effusions in otitis media with effusion: evidence for a different etiology. Laryngoscope 1997; 107:684-689.

Long JS, Freese J. Regression models for categorical dependent variables using stata. 2nd ed. Chapter 6. Stata Press, College Station. 2006.

Mandel EM, Rockette HE, Bluestone CD, et al. Efficacy of amoxicillin with and without decongestant-antihistamine for otitis media with effusion in children: results of a double-blind, randomized trial. N Eng J Med 1987; 316:432-437.

Mandel EM, Rockette HE, Paradise JL, Bluestone CD, Nozza RJ. Comparative efficacy of erythromycin-sulfisoxazole, cefaclor, amoxicillin of placebo for otitis media with effusion in children. Pediatr Infect Dis J, 1991; 10:899-906.

Mandel EM, Casselbrant ML Rockette HE, Bluestone CD, Kurs-Lasky M. Efficacy of antimicrobial prophylaxis for recurrent middle ear effusion: original studies. Pediatr Infect Dis J 1996; 15:1074-1082.

Rovers DM, Schilder AGM, Zielhuis GA, Rosenfeld RM. Otitis media: seminar. The Lancet, 2004; 363:1080.

Tran C. Update on otitis media: Grand rounds archives. Bobby R Alford department of otolaryngology-head and neck surgery, Baylor university. 2005. http://www.bcm.edu/oto/grand/pedioto.html

White H. Maximum likelihood estimation of misspecified models. Econometrica, 1982; 50, 1-25.

van Heerbeek N, Akkerman AE, Ingels K, Engel JAM, Zielhuis GA. Left-right differences in Eustachian tube function in children with ventilation tubes. Int J Pediatr Otorhinolaryngol 2003; 67:861-866.

Zeger SL & Qaqish B. Markov regression models for time-series: a quasi-likelihood approach. Biometrics. 1988; 44:1019-1031.