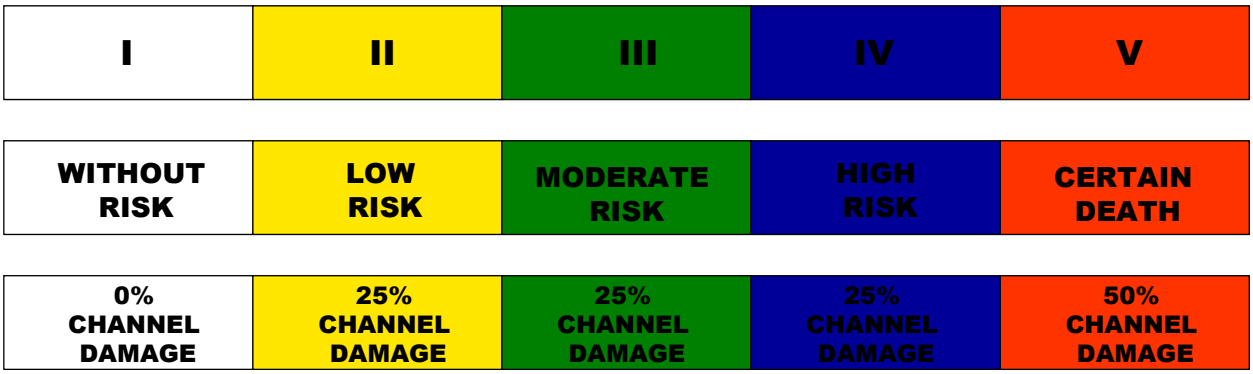
THE SPECTRUM OF CLINICAL PRESENTATION IN THE BRUGADA SYNDROME; NATURAL HISTORY AND THE PROGNOSIS

(Modificated From Pedro Brugada).



There are conflicting data about its prevalence and prognosis. Brugada-type ECG is much more prevalent than the manifest Brugada syndrome. Is the prognosis a manifestation of the degree of Na^+ channel damage?

I) Asymptomatic

The natural history of asymptomatic individuals with a Brugada-type ECG is still controversial.

(IA) Asymptomatic, normal ECG, only abnormal after drugs, no inducible by Programmed Electrical Stimulation (PES) and 0% channel damages. Same prognosis as normal individuals;

(1B) Asymptomatic, normal ECG (negative phenotype), only abnormal after drugs, no inducible by PES, 25% channel damages. Good prognosis, low risk if not exposed to pernicious drugs. Sodium channel-blocking antiarrhythmic drugs and tricyclic antidepressants should be avoided. These patients belong to the group of the "Silent mutation carrier" defined as any asymptomatic individual with an *SCN5A* mutation and normal ECG both at baseline and after pharmacological challenge;

(1C) Asymptomatic, spontaneous abnormal ECG and inducible by PES. 25% channel damage. These patients belong to the group of the "Silent mutation carrier" defined as any asymptomatic individual with an *SCN5A* mutation and normal ECG both at baseline and after pharmacological challenge: moderate risk;

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Imaki et al evaluated VF inducibility in Brugada-type ECG patients and compared it with other risk factors to clarify the significance of these data on their prognosis. The study population consisted of 38 patients who presented with a typical ST-segment elevation in the precordial leads and underwent an EPS. The patients were divided into 3 groups:
Group A: patients with spontaneous VF (n = 5);
Group B: patients without clinical VF but with inducible VF in EPS (n = 16);
Group C: patients with neither clinical nor inducible VF (n = 17).
The clinical features, diagnostic results, and prognosis were compared among these groups. During the follow-up period of 26 +/- 19 months, 2/5 (group A), 1/16 (group B), and 0/17 (group C) patients suffered fatal arrhythmic events. None of the clinical features showed any significant difference, although the incidence of positive results in a drug challenge test was higher in groups A and B than in group C ($P < 0.05$). On the other hand, VF inducibility was higher in patients with positive results in the drug challenge test than in patients with negative results (59% versus 13%; $P < 0.05$). No VF episodes were observed in patients without VF induction, although one was observed in 1 of 16 patients with VF induction in asymptomatic BrS. The drug challenge test appears to be useful for predicting VF inducibility even though it is a noninvasive test. **Imaki R, Niwano S, Fukaya H, Sasaki S, Yuge M, Hirasawa S, Sato D, Sasaki T, Moriguchi M, Izumi T.Predictive Impact of the**

Inducibility of Ventricular Fibrillation in Patients With Brugada-Type ECG. Int Heart J. 2006 Mar;47(2):229-36

II) Symptomatic individuals

IIA) Symptomatic (class III: syncope) abnormal ECG or drug-induced. 25% channel damage, high risk;

IIB) Symptomatic (class IV: individual resuscitated from IVF), spontaneous abnormal ECG, and 50% channel damage: certain death if not protected by an ICD.

The prognosis is poor for patients of groups IIA and IIB who do not receive an ICD.

THE PROGNOSIS

The poor prognosis is similar in patients with a history of aborted SCD (class IV) or syncope (class III) and in asymptomatic patients in whom the abnormal ECG characteristic of the syndrome was identified during a routine examination[1].
Those with a transiently concealed pattern had a 35% incidence of VF or SCD over a follow-up period of 43 ± 32 months.
The presence of an *SCN5A* mutation showed 32% sensitivity and 57% specificity to identify patients with cardiac arrest.

SYMPTOMATIC PATIENTS[2]

These have an unacceptably high rate of arrhythmic events. For both categories (Class III and IV) of symptomatic patients, the recurrence rates near a mean of 11% per

mean follow-up year 8.8% per year in Class III patients and 3.7% per year in patients resuscitated from SCD (class IV).

ASYMPTOMATIC PATIENS

1) Spontaneously abnormal type 1 ECG was recorded as part of a routine screening;

2) Abnormal ECG was obtained because of a family history of SCD;

3) Abnormal ECG type 1 appeared only during treatment with antiarrhythmic drugs given for the treatment of arrhythmias.
Asymptomatic individuals with a spontaneous abnormal type 1 ECG developed an arrhythmic event during a mean follow-up period of only 27±29 months. A "spontaneous pattern" is defined as an ECG showing the patterns established for the first European Consensus about the syndrome[3] classified the repolarization disorders occurred in the right precordial leads (V_1 and V_2) or in the anteroseptal wall (V_1 to V_3) in three types: **Wilde AA, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, Corrado D, Hauer RNm Kass RS, Nademanee K, Priori SG, Towbin JA. Proposed diagnostic criteria for the Brugada syndrome Eur Heart J 2002; 23:1648-1654.**

Type 1: ST-segment elevation coved to the top (“coved type”) = or > 2mm (0.2mV), and followed by negative T wave (Brugada phenotype);
Type 2: J point and ST segment elevation = or > 2mm (0.2mV) with saddleback appearance, followed by positive T wave; and
Type 3: J point and ST segment elevation < 1mm and with variable shape: whether coved type or saddleback appearance.

If the patient is asymptomatic and the ECG is normal (negative phenotype), the unmasking of the abnormal ECG with a drug identifies a carrier. Prof. Silvia Priori et al)[4-5] affirm that a negative phenotype (silent mutation carriers) or who have a diagnostic ECG only after provocative challenge are at lower risk of cardiac events: only **5%** of them had cardiac arrest in 4 decades of follow-up.
In symptomatic individuals (i.e., those who had experienced aborted SCD), the incidence of SCD on follow-up was similar to that reported by Brugada (i.e., 23% mortality rate during a mean follow-up interval of 33 to 38 months). The abnormality in *SCN5A* was demonstrable in only 15% of affected individuals. A positive electrophysiological study (i.e., one in which VT or VF was induced) had a positive predictive accuracy of 50%.
Pharmacological challenge with sodium channel blockers failed to unmask most silent gene carriers (positive predictive accuracy, 35%).

The clinical and follow-up of 25 to 30 month data of 50 patients (47 men, mean age, 53 years) were collected by Mok et al, in the Chinese population[6]. Additionally genetic data of 36 probands and eight family members of three genotyped probands were analyzed.
The patients were divided in three groups:

1) **Group A:** Survived SCD (eight patients): PES Positive inducible sustained ventricular arrhythmias: 88% and new arrhythmic events occurred in 50%;

2) **Group B**: 12 had syncope of unknown origin: Positive inducible sustained ventricular arrhythmias to PES: 82% and new arrhythmic events occurred in 17%;

3) **Group C:** Asymptomatic before recognition of Brugada syndrome (BS) (30 patients): Positive inducible sustained ventricular arrhythmias to PES: 27%. The patients remained asymptomatic during a

mean follow-up period of 25 (standard deviation, 11) months.

Five of 36 probands (14%) and three of eight family members who underwent genetic testing were found to have a mutation in their SCN5A gene.

The authors conclude that in the Chinese populations with BrS who are symptomatic there is a high likelihood of arrhythmia recurrence, whereas asymptomatic patients **enjoy a good short-term prognosis**.

The prevalence of SCN5A mutation among probands was 14%. Thus, Chinese patients with BS share with their western counterpart's similar clinical and genetic heterogeneity.

The authors do not make reference if the patients of Group C had spontaneous abnormal ECG.

Recently the Brugada brothers[7] analyzed a cohort of patients with BS without previous cardiac arrest to understand the determinants of prognosis. A total of 547 patients (408 male with mean age 41y) with an ECG diagnostic of BS and no previous cardiac arrest were studied. 124 patients had suffered from at least 1 episode of syncope.

The diagnostic ECG was present spontaneously in 391 patients. In the remaining 156 individuals, the abnormal ECG was noted only after the administration of an antiarrhythmic drug. During PES, a sustained PTV/VF was induced in 163 of 408 patients. During a mean follow-up of 24+/-32 months, 45 patients (8%) suffered SCD or documented VF. Multivariate analysis identified the inducibility of a sustained PVT/FV ($P<0.0001$) and a history of syncope ($P<0.01$) as predictors of events. Logistic regression analysis showed that a **patient with a spontaneously abnormal ECG, a previous history of syncope, and inducible sustained ventricular arrhythmias had a probability of 27.2% of suffering an**

event during follow-up. The Brugada brothers conclude that the individuals with BrS and no previous cardiac arrest have a high risk of SCD. Inducibility of ventricular arrhythmias and a previous history of syncope are markers of a poor prognosis.

The prognosis of patients with the syndrome of RBBB and ST segment elevation in V1-V2 (BS) has been controversial, for asymptomatic individuals. There was a report on the largest cohort of patients with BrS and the prognostic significance of clinical and electrophysiological data was analyzed.

A total of 667 patients with the ECG characteristics of BrS were analyzed by the Brugada brothers[-8-9].

Mean age at diagnosis was 41±15 years, 507 were male. The diagnosis was made due to the presence of a basal diagnostic ECG in 499 patients and in 168 the diagnostic ECG was noted only after antiarrhythmic drug administration. Sustained ventricular arrhythmias were induced during electrophysiological study in 231 out of 493 patients. During their lifetime patients a 25% presented at least one episode of SCD or documented VF at a mean age of 43±15 years (2 to 77 years).

Using multivariate Cox regression models, inducibility of sustained ventricular arrhythmias ($p<0.0001$, Hazard ratio 3.8, 95% CI 2.4-6.25), a male gender ($p<0.02$, Hazard ratio 1.9, 95% CI 1.03-3.4) and a basal abnormal ECG ($p<0.05$, Hazard ratio 1.9, 95% CI 1.01-3.7) were all predictors of occurrence of SCD or VF. Using a logistic regression model, the probability that a male, with a basal abnormal ECG and inducible has an event is 45% (CI 38-53%).

The following are markers of a poor prognosis**:**

1) Patients with an a spontaneously abnormal ECG showing RBBB or not and J point and ST segment elevation (≥2 mm) coved to the top followed by negative T wave in the right precordial;

2) Prolonged QRS duration in precordial leads is prominent in symptomatic patients. This ECG marker may be useful for distinguishing high- from low-risk patients with BrS. (**Takagi M, Yokoyama Y, Aonuma K, Aihara N, Hiraoka M; for the Japan Idiopathic Ventricular Fibrillation Study (J-IVFS) Investigators. Clinical Characteristics and Risk Stratification in Symptomatic and Asymptomatic Patients with Brugada Syndrome: Multicenter Study in Japan. J Cardiovasc Electrophysiol. 2007** 2007 Dec;18(12):1244-51. Patients with inducibility of sustained ventricular arrhythmias at PES: Concensus does not exist on the value of PES to identify the subjects with risk of pontaneous occurrence of VF. Brugada brothers think that theses patients should receive an ICD.(**Brugada P, Brugada R, Mont L, Rivero M, Geelen P, Brugada J. Natural history of Brugada syndrome: the prognostic value of Programmed electrical stimulation of the heart. J Electrophysiol 2003; 14: 455-457.) (Brugada J, Brugada R, Brugada P. Right bundle-branch block and ST-segment elevation in leads V1 through V3: a marker for sudden death in patients without demonstrable structural heart disease. *Circulation.* 1998; 97: 457–460.**) On the other hand, Priori et al from 200 patients using the life-table method of Kaplan-Meier used to define the cardiac arrest-free interval in patients undergoing PES failed to demonstrate an association between PES inducibility and spontaneous occurrence of VF[5]; **Priori SG, Napolitano C, Gasparini M, et al. Natural history of Brugada syndrome: insights for risk stratification and management. Circulation. 2002; 105: 1342-1347.**
3) Male gender predict a more malignant natural history;
4) Symptomatic patients: A history of syncope or aborted sudden death is predictor of adverse outcome.

5) Spontaneous ST-segment elevation in leads V_1 through V_3 combined with the history of syncope is a powerful marker to identify individuals who had cardiac arrest.
6) A spontaneous change in ST segment is associated with the highest risk for subsequent events in subjects with a Brugada-type 1 ECG. The presence of syncopal episodes, a history of familial sudden death, and/or LP may increase its value. **Ikeda T, Takami M, Sugi K, Noninvasive risk stratification of subjects with a Brugada-type electrocardiogram and no history of cardiac arrest. Ann Noninvasive Electrocardiol. 2005;10:396-403.**
7) A history of syncope or SCD, the presence of a spontaneous Type 1 Brugada ECG, and male gender predict a more malignant natural history. The use of a family history of SCD, the presence of an SCN5A gene mutation, or EPS to guide the management of patients with a Brugada ECG is not supported. **Gehi AK, Duong TD, Metz LD, et al. Risk stratification of individuals with the brugada electrocardiogram: a meta-analysis. J Cardiovasc Electrophysiol. 2006;17:577-583.** A genetic defect on the *SCN5A* gene is not associated with a higher risk of events, suggesting that genetic analysis is a most useful diagnostic parameter but it is not helpful for risk stratification(**Priori SG, Napolitano C, Gasparini M, et al. Natural history of Brugada syndrome: insights for risk stratification and management. Circulation. 2002; 105: 1342-1347.**)

MORTALITY AT FOLLOW-UP OF ASYMPTOMATIC PATIENTS WITH BRUGADA SYNDROME

Author	Number of Patients asymptomatic	Year	Follow up (y)	SCD rate
Atarashi H[12]	34	1996	1-3	0%
Priori SG[4]	30	2000	1-3	0%
Atarashi H[13]		2001		
Takenaka S[13]	11	2001	3-4	0%
Miyasaka Y[14]	98	2001	2,6	1%
Matsuo K[15]	32	2001	1-14	22,4
Priori SG[5]	144	2002	10	19% (14% + 5%)*
Brugada J[8]	111	2002	3	14%
Brugada J[7]	423	2003	2	
Mok NS[6]	30	2004	2	0%

* Patients with a spontaneous ST-segment elevation ≥2 mm without history of syncope. This group included 41% of patients, and 14% of them had cardiac arrest: they are a group at intermediate risk, and their treatment is undetermined. Patients with a negative phenotype (silent mutation carriers) or who have a diagnostic ECG only after provocative challenge are at lower risk of cardiac events: They represent 49% of the population, and only 5% of them had cardiac arrest in 4 decades of follow-up.

CONTROVERSIAL POINTS WITHOUT CONSENSUS

	Brugada Group	Priori Group
		(**Priori SG, Napolitano C, Gasparini M, et al. Natural history of Brugada syndrome: insights for risk stratification and management. Circulation. 2002; 105: 1342-1347**.).

PES inducibility identify high-risk subjects **Predictive value of PES in BrS:**	**Yes. Inducibility at PES identifies high-risk subjects who should receive an ICD. Brugada P, Brugada R, Mont L, Rivero M, Geelen P, Brugada J. Natural history of Brugada syndrome: the prognostic value of Programmed electrical stimulation of the heart. J Electrophysiol 2003; 14: 455-457.**	**No. PES failed to demonstrate an association between PES inducibility and spontaneous occurrence of VF. (Priori SG, Napolitano C, Gasparini M, et al. Natural history of Brugada syndrome: insights for risk stratification and management. Circulation. 2002; 105: 1342-1347.). (Eckardt L, Probst V, Smits JP, Bahr ES, Wolpert C, Schimpf R, Wichter T, Boisseau P, Heinecke A, Breithardt G, Borggrefe M, Lemarec H, Bocker D, Wilde AA. Long-Term Prognosis of Individuals With Right Precordial ST-Segment-Elevation Brugada**

Basal abnormal type 1 ECG in asymptomatic patients:	Predictor of occurrence of SCD or VF. These patients are candidates for an ICD.	Non-predictor of occurrence of SCD or VF. Treatment is undetermined.
Male gender is predictor of poor prognosis:	Yes.	No.

Eckardt et al (**Eckardt L, Probst V, Smits JP, Bahr ES, Wolpert C, Schimpf R, Wichter T, Boisseau P, Heinecke A, Breithardt G, Borggrefe M, Lemarec H, Bocker D, Wilde AA. Long-Term Prognosis of Individuals With Right Precordial ST-Segment-Elevation Brugada Syndrome.Circulation. 2005; 111: 257-262**) studied during a mean follow-up of 40 months a numerous universe of a collaborative large cohort 212 individuals who presented Brugada type 1 electrocardiographic pattern, from which 125 (59%) was spontaneous, and the rest only after pharmacological test with a class I drug.

The authors verified that 58% were asymptomatic; 31% had suffered >/= 1
episodes of syncope with unknown origin and 11% had been resuscitated from a
VF episode (aborted sudden death).

A history of syncope or aborted sudden death was predictor of adverse outcome.

The degree of elevation of the T segment was greater between symptomatic
individuals: 2.3 mm higher than asymptomatic ones (mean 1.9 mm).

In the latter, it was observed that the incidence of events was very low, and PES
had a very low accuracy in predicting evolution. This paper attempts to

clarify the controversial issue, which still persists, between Priori's
group and Brugada's group, regarding the predictive value of PES, agreeing
with the former. The data regarding the risk of events in patients with Brugada syndrome are controversial and depend on the cohort of patients studied. This collaborative paper describes long-term follow up of a large cohort of well-identified Brugada syndrome patients as well as explores predictive value of PES. In contrary to some previous papers on the topic, in this study the authors could not demonstrate significant prognostic value of PES testing. The risk of arrhythmic events in asymptomatic patients is very low indicating that they could be considered as patients of much lesser risk than it was previously considered. This observation might have impact on both diagnostic triage and therapy approach in Brugada syndrome patients (pharmacological approach).

Paul et al in recent a meta-analysis of worldwide published data studied the significance role of PES for risk stratification in patients with BrS. (**Paul M, Gerss J, Schulze-Bahr E, Wichter T, Vahlhaus C, Wilde AA, Breithardt G, Eckardt L. Role of programmed ventricular stimulation in patients with Brugada syndrome: a meta-analysis of worldwide published data. Eur Heart J. 2007 May 5; [Epub ahead of print]**
A Medline((R)) search until July 2006 documented 822 entries for BrS. Only English publications with >10 patients and a follow-up period were considered (n = 15).

Patients [n = 1217; 974 males (80%)] were divided into three groups:

1) Survived sudden cardiac arrest [n = 222] (18%)
2) Syncope (Syncope) [n = 275] (23%);
3) Asymptomatic patients [n = 720] (59%).

PES was conducted in 1036 patients (85%). In 548 patients (53%), sustained VT or VF was inducible. During follow-up (34 +/- 40 months), VT/VF occurred in 141 patients.
Survived sudden cardiac arrest bore the highest chance for a VT/VF occurrence during follow-up [odds ratio (OR) 14.4 compared with asymptomatic patients; P < 0.0005]. However, except for one study, the OR for VT/VF during follow-up in relation to VT/VF inducibility was non-significant (OR 1.5; P = ns).
The authors conclude that the main finding is that we were unable to identify a significant role of PES with regard to arrhythmic events during follow-up in BrS, thus questioning the role of PES for risk stratification in patients with BrS.
In a meta-analysis 30 prospective studies of patients with the Brugada ECG, accumulating data on 1,545 patients a history of syncope or SCD, the presence of a spontaneous Type1 Brugada ECG, and male gender predict a more malignant natural history. A family history of SCD, the presence of an SCN5A gene mutation, or EPS to guide the management of patients are not predictives.**Gehi Ak, Duong TD, Metz LD, Gomes JA, Mehta D. Risk stratification of individuals with the Brugada electrocardiogram: a meta-analysis. J Cardiovasc Electrophysiol. 2006;17:577-583**

Patients with BrS and survived sudden cardiac arrest shows the highest chance for VT/VF occurrence during follow-up.

The Brugada phenotype ECG) is much more prevalent than the manifest BrS. Although invasive electrophysiologic investigations have been proposed as a risk stratifier, their value is controversial, and alternative noninvasive techniques may be preferred.

Ikeda et al sought a noninvasive strategy to detect a high-risk group in a long-term follow-up study of subjects with a Brugada-type ECG, and no history of cardiac arrest. The

study enrolled 124 consecutive subjects with a Brugada-type ECG. Prognostic indices included: age; sex, a family history of SCD, syncopal episodes, a spontaneous coved-type ST-segment elevation, maximal magnitude of ST-segment elevation, a spontaneous change in ST segment, a mean QRS duration, maximal QT interval, QT dispersion, late potentials (LP) by signal-averaged ECG, and microvolt T-wave alternans.

Of the 124 subjects, 20 consenting subjects had an ICD before follow-up. During a 40 +/- 19-month follow-up, 12 subjects (9.7%) reached one of the endpoints (SCD or VT). Of the 12 risk indices, a **family history of SCD, syncopal episodes, a spontaneous coved-type ST-segment elevation, a spontaneous change in ST segment, and LP** had significant values. In multivariate analysis, a spontaneous change in ST segment had the most significance (a relative hazard, 9.2; P = 0.036). Combined assessment of this index and other significant indices obtained higher positive predictive values (43-71%). The authors concluded that a spontaneous change in ST segment is associated with the highest risk for subsequent events in subjects with a Brugada-type ECG. The presence of syncopal episodes, a history of familial sudden death, and/or LP may increase its value.

Risk stratification of asymptomatic patients with Brugada type ECG is still a challenge. In particular, the use of EPS for risk stratification remains controversial. Although some investigators have reported the possibility of use of EPS for distinguishing between high- and low-risk patients with Brugada type ECG, no precise predictor of risk for SCD in asymptomatic patients has yet been determined. The approach to treatment of these patients is thus still unclear. Large clinical prospective studies with uniform diagnostic criteria and protocols for EPS as well as extended follow-up periods of over ten years are required for prediction of SCD.
Takagi M, Tatsumi H, Yoshiyama M.Approach to the asymptomatic patients with Brugada syndrome. Indian Pacing Electrophysiol J. 2007 Apr 1; 7(2):73-76.

34 patients with a Brugada-type ECG were enrolled by Ohkubo et a.. Twelve patients had a type 1 ECG, 12 had a type 2 ECG, and 10 had a type 3 ECG. PVS was performed with up to 2 ventricular premature beats from the RV apex and RVOT tract at 2 basic cycle lengths (600 and 400 ms). VF was induced in 17 of 23 (74%) asymptomatic patients and 10 of 11 (91%) symptomatic patients ($p<0.05$). The 27 patients in whom VF was induced by PVS and 7 patients without inducible VF were followed up for 47.1+/-33.7 months. One SD occurred during the follow-up period among asymptomatic patients with inducible VF, and no SD occurred among patients without inducible VF. Inducibility of ventricular arrhythmia is high in patients with BrS, but it does not correlate with clinical presentation. The PVS study-induced VF does not predict arrhythmic events during follow up. **Ohkubo K, Watanabe I, Takagi Y, Okumura Y, Ashino S, Kofune M, Kawauchi K, Yamada T, Kofune T, Hashimoto K, Shindo A, Sugimura H, Nakai T, Saito S, Hirayama A. Electrocardiographic and electrophysiologic characteristics in patients with brugada type electrocardiogram and inducible ventricular fibrillation. Circ J. 2007 Sep; 71(9): 1437-1441.**