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DECREASING FREQUENCY OF PLASMA EXCHANGE COMPLICATIONS IN PATIENTS TREATED FOR THROMBOTIC THROMBOCYTOPENIA PURPURA – HEMOLYTIC UREMIC SYNDROME, 1996-2011

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Abstract

BACKGROUND—Plasma exchange (PEX) treatment for patients with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS) has risk for major complications.

STUDY DESIGN AND METHODS—Data for PEX-related complications have been prospectively collected on all patients enrolled in the Oklahoma TTP-HUS Registry, 1996-2011. PEX-related complications have been defined as major or minor and as central venous catheter-related or plasma-related.

RESULTS—During 15 years, 1996-2011, 72 (24%) of 302 consecutive patients had major PEX-related complications. Analysis of five consecutive three-year cohorts demonstrated that there has been a significant trend for decreasing frequency of all PEX-related major complications (P=0.014) and central venous catheter-related major complications (P=0.021) but not for the less common plasma-related major complications (P=0.380). ADAMTS13 activity was measured in 288 (95%) of the 302 patients. Analysis of the 66 patients with ADAMTS13 activity <10% demonstrated a significant trend for decreasing frequency of PEX-related major complications (P=0.036); the trend for the 222 patients with ADAMTS13 activity ≥10% was not significant (P=0.118). The decreased frequency of PEX-related major complications among patients with ADAMTS13 activity <10% may be related to a significant trend for decreasing duration of PEX treatment (P=0.040) and decreasing frequency of requirement for more than one central venous catheter (P=0.044). The decreased duration of PEX treatment may be related to increased use of adjunctive treatments: corticosteroids (P<0.001) and rituximab (P<0.001).

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CONCLUSIONS—The frequency of PEX-related major complications has decreased from 1996 to 2011, possibly related to increased use of corticosteroids and rituximab and the decreased duration of PEX required to achieve remission.

INTRODUCTION

Because of the frequent uncertainty about the initial diagnosis of thrombotic thrombocytopenic purpura-hemolytic uremic syndrome (TTP-HUS), the potential benefits and risks of plasma exchange (PEX) treatment are critical considerations for management decisions. To document PEX-related complications, the Oklahoma TTP-HUS Registry has prospectively assessed all PEX procedures for all patients treated for clinically diagnosed TTP or HUS since 1996. In our initial report of the Registry experience, 1996-1999,[1] and in subsequent reports of the successive three-year cohorts of our experience, 1999-2008,[2-4] we described the occurrence of major complications and deaths attributed to PEX treatment. In the analysis of our current data, 2008-2011, we discovered an unexpected trend for decreasing PEX-related complications across our 15 year experience. In this report we describe the occurrence of PEX-related major complications across 15 years in all patients and also in patients with and without severe ADAMTS13 deficiency. We also describe the changes of patient management that have occurred during these 15 years and that may have contributed to the decreasing frequency of PEX-related complications.

METHODS

Patients

The Oklahoma TTP Registry, established January 1, 1989, is an inception cohort of consecutive patients with a diagnosis of TTP or HUS.[5,6] Patients are identified by a request to the Oklahoma Blood Institute (OBI) for plasma exchange treatment. The OBI is the sole provider of plasma exchange treatment for all hospitals in the 58 of Oklahoma's 77 counties; these 58 counties, with a population of 2,310,000 in 2000, comprise the Registry region. Since standard practice in this region is to treat all adults who are diagnosed with either TTP or HUS, as well as all children who are diagnosed with TTP, with plasma exchange, the Registry is a population-based inception cohort of consecutive patients in whom a diagnosis of TTP or HUS is made and plasma exchange treatment is requested.[5,6] Plasma exchange procedures are performed in one of twelve hospitals in the Oklahoma City metropolitan area. Patients initially diagnosed in another region of the state are transferred to one of these hospitals for plasma exchange treatment. The Registry is approved by the institutional review boards of the University of Oklahoma Health Sciences Center and each participating hospital.

Plasma exchange procedures

All PEX procedures are performed in a consistent manner by one of the nurses on the Hematopoietic Progenitor Cells (HPC)/Therapeutic Services staff of the OBI. The nurses go to the patient's hospital, bringing with them the OBI's apheresis instrument and equipment. OBI staff nurses are available at all times to initiate PEX. The instruments used are either COBE® Spectra or Spectra Optia® Apheresis Systems (CaridianBCT, Lakewood, CO). All procedures follow protocols developed by Ms. Mandi Kaiser, RN, HP (ASCP), HPC/ Therapeutic Services Nurse Manager. These protocols address all aspects of the plasma exchange procedures. They outline details of procedure for operating the Apheresis Systems and the Ranger® Blood/Fluid Warming Systems, for monthly quality control of the instruments when all pressure pods and other components are inspected and appropriately replaced, for management of the central venous catheter, and for aseptic technique. For patients with a diagnosis of TTP or HUS, PEX is performed with one plasma volume of

either cryosupernatant plasma, 24 hour plasma, or fresh-frozen plasma, whichever product is most accessible from the OBI inventory. Plasma is anticoagulated with ACD-A; calcium is replaced only for symptoms of hypocalcemia.

Patient management

In contrast to the consistent methods for performance of PEX procedures, management decisions are made by each patient's primary physician. The role of the Registry is only to provide advice and support for the primary physician (typically a hematologist or nephrologist) and also for the patient, as well as to collect data.[7] The 302 patients in this study were primarily cared for by 96 different physicians in 12 different hospitals in the Oklahoma City metropolitan area; these data emphasize the potential for multiple varieties of management. These physicians determine the methods for venous access in consultation with their hospital's surgeons or interventional radiologists. They also make the initial treatment decisions, including the decision to use corticosteroids. Subsequent management decisions, such as the use of rituximab and the stopping and/or tapering of PEX are often made during discussions with one of the authors (JNG, who saw and was involved in the care of 285 (94%) of these 302 patients). The Registry has no protocols for the use of adjunctive treatments (corticosteroids, rituximab) and the stopping and/or tapering of PEX, and community practice has changed during the past 15 years. Recent common community practice is to treat with corticosteroids when there is no apparent additional or potential alternative disorder contributing to the patient's clinical features and to treat with rituximab when the patient has a prolonged clinical course, such as the occurrence of new neurologic abnormalities or the recurrence of thrombocytopenia after PEX has begun.[8] Rituximab is also used for patients with relapsed episodes. Current community practice is to stop plasma exchange without tapering for all patients, unless exacerbations have occurred. For patients with exacerbations, in whom daily PEX has had to be resumed,[5] tapering is considered when a response occurs and stopping PEX is appropriate.

ADAMTS13 activity measurements

Serum samples have been obtained immediately before the first plasma exchange treatment beginning on November 13, 1995. ADAMTS13 activity measurements are performed in the Central Hematology Laboratory of the Inselspital, Berne, Switzerland by both quantitative immunoblotting of degraded, plasma-derived von Willebrand factor substrate[9,10] and a fluorogenic assay using FRETS-VWF73 substrate.[11,12] Patients are designated as having severe ADAMTS13 deficiency when measurement by either method was <10%.[6] Assays of ADAMTS13 activity are performed without knowledge of the patients' clinical data. The initial decision to request plasma exchange treatment is almost always made without knowledge of the patients' ADAMTS13 activity because from our community the test must be sent to a reference laboratory.

PEX complications

Beginning on June 25, 1996, all complications at the time of every PEX procedure were prospectively documented by the OBI nurse. PEX-related complications were also documented by one of the authors (J.N.G.) when they occurred before the PEX procedures began, such as during the central venous catheter insertion procedure, or after the PEX procedures were stopped, such as central venous catheter-related sepsis and venous thrombosis. In the initial report of our experience[1] we defined PEX-related complications as major if: [1] additional hospitalization or transfer to an intensive care unit, [2] an invasive procedure (such as replacement of a central venous catheter), [3] a new systemic treatment (other than diphenhydramine, hydrocortisone, or $CaCl_2$), or [4] a red cell transfusion was required, or [5] the PEX treatment had to be stopped.[1] Complications were further

distinguished as related to either [1] the central venous catheter or [2] the infused plasma.[1] Minor complications have been previously defined.[1]

Statistical analysis

Only data from each patient's first episode were analyzed. Major complications were evaluated for all patients and also for patients stratified by ADAMTS13 activity (<10% versus ≥10%). Trends of frequency were analyzed across the five consecutive three-year cohorts, 1996-2011. Data from the first four cohorts have been previously published;[1-4] data from the fifth cohort, 2008-2011, are presented in this analysis. A one-sided Cochran-Armitage Trend test was performed to determine if the proportion of patients with major complications (central venous catheter-related only, plasma-related only, or combined) or the proportion of patients who required more than one central venous catheter placement decreased across the five time periods. Some patients experienced both central venous catheter-related and plasma-related complications and were therefore included in both analyses. An exact test was performed if sample size assumptions for the asymptotic one-sided Cochran-Armitage Trend test were not met. A one-sided Jonckheere-Terpstra test was performed to evaluate if the median number of days of PEX decreased across the five time periods. The proportion of patients who required more than one central venous catheter insertion and the median number of days of PEX were only evaluated in the patient groups stratified by ADAMTS13 activity. An alpha of 0.05 was used. Analyses were performed using SAS, version 9.2.

RESULTS

PEX complications, 2008-2011

During the most recent three year period, eight (17%) of 53 patients had 11 major complications; no patients died as a result of these complications (Table 1). Seven patients had eight central venous catheter-related major complications. Two had failed central venous catheter insertions requiring immediate catheter replacement. One of these two patients and four additional patients developed sepsis attributed to their central venous catheters: two with *Staphylococcus epidermidis* and one each with methicillin-resistant *Staphylococcus aureus, Corynebacterium amycolatum*, and *Streptococcus salivarius*. One patient developed a large hematoma at the femoral catheter insertion site causing cancellation of her final PEX treatment. Two of these seven patients and one additional patient each had a major plasma-related complication. Two had acute respiratory distress with throat tightness and hypoxia that required respiratory therapy; one had fluid overload requiring intubation and ventilation; in all three patients the PEX procedure had to be stopped. Eighteen (34%) patients had one or more minor complications, including three patients who also had major complications. The majority of minor complications were urticaria (12 patients); other minor complications included dyspnea responding to nasal cannula oxygen and hypotension responding to administrations of intravenous fluids. Thirty (57%) patients had no major or minor complications.

PEX complications, 1996-2011

During all 15 years, 1996-2011, we have observed 94 major complications of plasma exchange in 72 (24%) of 302 consecutive patients treated for their first episode of clinically diagnosed TTP; the complications were fatal in 7 (2.3%) patients (Table 1). Central venous catheter-related complications were more common as well as more critical than plasma-related major complications. It was apparent that the percent of patients with major complications attributed to PEX had decreased across these 15 years (Table 2). The decreased frequency of major complications was the result of a decreased frequency of central venous catheter-related complications rather than plasma-related complications.

PEX complications, 1996-2011: comparison of patients with ADAMTS13 activity <10% to patients with ADAMTS13 activity ≥10%

During these 15 years, ADAMTS13 activity was measured in 288 (95%) of the 302 patients. Data are presented separately for the 66 patients with ADAMTS13 activity <10% (Table 3) and the 222 patients with ADAMTS13 activity ≥10% (Table 4). Among patients with ADAMTS13 activity <10%, the frequency of patients with major complications, including both catheter-related or plasma-related complications, significantly decreased. Although the frequency of all major complications, both catheter-related and plasma-related, also appeared to decrease among patients with ADAMTS13 activity ≥10%, the trend was not significant. When catheter-related and plasma-related major complications were analyzed separately for patients with ADAMTS13 activity <10% or ≥10%, the frequency of catheter-related major complications appeared to decrease but the trend was not significant.

Duration of PEX treatment and frequency of required central venous catheter replacement, 1996-2011

The duration of PEX treatments, defined as the number of days between the first and last PEX treatments, significantly decreased for patients with ADAMTS13 activity <10%; the decrease was not significant for patients with ADAMTS13 ≥10% (Table 5). One reason for the decreased duration of PEX treatments was the decreased frequency of tapering PEX once a response has occurred. The frequency of tapering significantly decreased across the five cohorts in both patients with ADAMTS13 activity <10% than for patients with ADAMTS13 activity ≥10%, however within each cohort the frequency of tapering was greater for patients with ADAMTS13 activity <10%. Both groups of patients have required central venous catheter replacement significantly less often in more recent years, consistent with the decrease of PEX treatment duration.

Frequency of treatment with corticosteroids and rituximab, 1996-2011

The frequency of treatment with corticosteroids significantly increased for patients with ADAMTS13 activity <10%; there was no significant trend for patients with ADAMTS13 ≥10% (Table 6). Rituximab was first used for treatment of patients with TTP-HUS in 2003. The frequency of treatment with rituximab significantly increased for both groups of patients (ADAMTS13 activity <10% and ≥10%).

DISCUSSION

Awareness of the risks of PEX treatment is important for management of patients in whom the diagnosis of TTP-HUS is considered. Across the first 9 years of our experience, 1996-2005, we documented major complications of PEX treatment in 26-30% of patients, including deaths attributed to PEX treatment in five (2.4%) patients.[1-3] This frequency of major complications was much greater than in other reports in which severe complications and deaths attributed to PEX were described as rare.[13-16] The difference may be related to our method of prospectively and systematically documenting the outcome of each PEX procedure on every patient for whom PEX is requested for a diagnosis of TTP or HUS, beginning with the insertion of the central venous catheter before PEX was begun and continuing after PEX treatments were stopped. For example, this comprehensive surveillance allows us to identify complications of central venous catheter insertion before the OBI apheresis nurses become involved in the patient's care and to identify late complications attributed to the central venous catheter which may occur after PEX treatment is completed, when OBI apheresis nurses are no longer involved in the patient's care. Complications such as venous thrombosis at the catheter site, sometimes in association with bacterial sepsis, may occur after the patient is discharged from the hospital requiring readmission to a hospital.

In our fourth cohort of patients, 2005-2008, the frequency of major PEX-related complications had decreased to 16%, but still two deaths occurred which continued to emphasize the clinically important risks of PEX treatment for patients with TTP-HUS.[4]

Only during the analysis of our fifth and current cohort of patients, 2008-2011, did we recognize the trend for decreasing frequency of PEX complications. Also this was the first cohort in which no deaths were attributed to PEX complications. Across the entire 15 year experience with five cohorts of patients, the trend for decreasing frequency of all PEX-related major complications and central venous catheter-related major complications, but not plasma-related major complications, was significant. The trend for decreasing frequency of central venous catheter-related major complications may be related to significant trends for decreasing duration of PEX treatments and for decreasing requirement for replacement of the central venous catheter.

Decreased duration of PEX treatment, defined as the number of days between the first and last PEX treatments, has probably occurred for two reasons. First, at the beginning of this 15 year experience, we commonly continued PEX treatment after the platelet count recovered to normal by tapering the frequency of PEX procedures. We did not stop PEX treatment abruptly because of the potential for exacerbation of TTP when PEX was stopped.[17] Our current practice is to stop PEX treatments abruptly when the platelet count recovers to normal because of our recent experience that abruptly stopping PEX was not followed by exacerbation in most patients.[8]

The second reason for the decreased duration of PEX treatment may be our more consistent use of adjunctive treatments with corticosteroids and rituximab, which may also be the reason for less frequent exacerbations among patients with ADAMTS13 activity <10%.[8] At the beginning of this 15 year experience, we typically initiated PEX treatment without additional corticosteroid treatment for all patients with suspected TTP or HUS.[17] Now we immediately begin corticosteroid treatment for all patients whose clinical presentation suggests severe ADAMTS13 deficiency.[8] The clinical features that suggest the presence of severe ADAMTS13 deficiency are the occurrence of thrombocytopenia and microangiopathic hemolytic anemia in a previously well patient and the absence of severe renal failure. The steroid regimen that is typically used is related to the severity of the patient's condition; often oral prednisone (1 mg/kg/day) is used but when a patient appears to be severely ill, higher doses of intravenous methylprednisolone are used (1000 mg/day for 3 days) followed by oral prednisone (1 mg/kg/day) or its equivalent as parenteral corticosteroid.[8] Our use of rituximab for treatment of TTP began 2003; it has increased steadily since that time.[8]

There may be two other reasons for the decreased frequency of central venous catheter-related major complications. First, ultrasound guidance of central venous catheter placement has become the standard of practice and this may have resulted in a decreased frequency of complications.[18,19] Second, hospitals have increased their focus on the prevention of nosocomial infections with greater emphasis on sterile techniques.[20,21] These changes have probably occurred in our community across the 15 years of our studies, but we have no data to quantify the change.

The frequency of patients with ADAMTS13 activity <10% who had no major PEX-related complications has increased, consistent with the decreased duration of PEX treatments required to achieve a remission. These changes may be related to increased use of adjunctive treatments, corticosteroids and rituximab, and also to the increased frequency of stopping PEX treatments abruptly rather than tapering the frequency of PEX treatments before stopping. These observations emphasize the importance of continued development of

effective adjunctive treatment regimens for TTP in order to decrease the requirement for PEX even further and thereby decrease the occurrence of PEX-related morbidity and mortality.

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Table 1

Major complications of plasma exchange treatment in patients with their initial episode of clinically diagnosed TTP-HUS

The definition of major complications and the classification of complications as central venous catheter-related or plasma-related have been previously described[1]

Major Complications	5th Cohort 2008-2011 (n = 53)	All Patients 1996-2011 (n = 302)
Catheter-related major complications		
Death	0	7
Pulmonary hemorrhage and pneumothorax	0	3
Systemic infection	0	4
Non-fatal complications	8	67
Systemic Infection	5	34
Documented bacteremia	5	29
Suspected bacteremia[1]	0	3
Fungemia	0	2
Local infection at catheter insertion site[2]	1	2
Thrombosis	0	22
Catheter obstruction[2]	0	17
Venous thrombosis requiring systemic anticoagulation	0	5
Pulmonary hemorrhage	0	2
Retroperitoneal hemorrhage	0	1
Catheter insertion site hemorrhage[3]	1	2
Pericardial tamponade	0	1
Pneumothorax[4]	0	2
Insertion of incorrect catheter[2]	1	1
Plasma-related major complications (none were fatal)		
Hypotension requiring dopamine	0	7
Anaphylaxis with cardiac arrest	0	1
Serum sickness	0	2
Hypoxia[5]	2	8
Vomiting[5]	0	1
Fluid Overload[6]	1	1

[1] Negative blood cultures but treatment with a full course of parenteral antibiotics for presumed sepsis

[2] Required removal of the catheter and placement of a new catheter

[3] Required red cell transfusion

[4] Required placement of a chest tube

[5] Required stopping plasma exchange

[6] Required stopping plasma exchange, intubation, and ventilation therapy

Table 2

Frequency of major complications of plasma exchange treatment in all 302 patients with their initial episode of clinically diagnosed TTP-HUS, 1996-2011

Cohort		Total patients	Patients with major complications*			Patient deaths		
			Total	CVC-related	Plasma-related	CVC-related		Plasma-related
						Insertion	Sepsis	
1	1996-1999	71	21 (30%)	19 (27%)	3 (4%)	1	1	0
2	1999-2002	78	21 (27%)	16 (21%)	7 (9%)	1	0	0
3	2002-2005	57	15 (26%)	12 (21%)	3 (5%)	1	1	0
4	2005-2008	43	7 (16%)	6 (14%)	1 (2%)	0	2	0
5	2008-2011	53	8 (15%)	7 (13%)	3 (6%)	0	0	0
P			0.014	0.021	0.380			

*Data presented are for the number of individual patients, in contrast to Table 1 which presents data for the number of individual complications. Some patients had more than one major complication. Some patients had both central venous catheter (CVC)-related and plasma-related major complications

Table 3

Frequency of major complications of plasma exchange treatment in all 66 patients with ADAMTS13 activity <10% during their initial episode of clinically diagnosed TTP-HUS, 1996-2011

Cohort		Total patients	Patients without major complications	Patients with major complications*		
				Total	CVC-related	Plasma-related
1	1996-1999	11	5 (45%)	6 (55%)	5 (45%)	2 (18%)
2	1999-2002	20	11 (55%)	9 (45%)	7 (35%)	3 (15%)
3	2002-2005	10	4 (40%)	6 (60%)	5 (50%)	1 (10%)
4	2005-2008	15	11 (73%)	4 (27%)	4 (27%)	0
5	2008-2011	10	8 (80%)	2 (20%)	2 (20%)	1 (10%)
P			0.036		0.123	0.135

*Some patients had both central venous catheter (CVC)-related and plasma-related major complications

Table 4

Frequency of major complications of plasma exchange treatment in all 222 patients with ADAMTS13 activity ≥10% during their initial episode of clinically diagnosed TTP-HUS, 1996-2011

Cohort		Total patients	Patients without major complications	Patients with major complications*		
				Total	CVC-related	Plasma-related
1	1996-1999	54	42 (78%)	12(22%)	11 (20%)	1 (2%)
2	1999-2002	53	43 (81%)	10(19%)	8 (15%)	3 (6%)
3	2002-2005	47	38 (81%)	9(19%)	7 (15%)	2 (4%)
4	2005-2008	27	24 (89%)	3 (11%)	2 (7%)	1 (4%)
5	2008-2011	41	35 (85%)	6 (15%)	5 (12%)	2 (5%)
P			0.118		0.086	0.307

*Some patients had both central venous catheter (CVC)-related and plasma-related major complications

Table 5

Decreasing exposure to risk for central venous catheter-related complications in 5 cohorts of patients treated with plasma exchange for TTP-HUS, 1996-2011

Cohort		Exposure to Central Venous Catheter (CVC)					
		Days of PEX[1] median (minimum, maximum)		Patients who completed PEX by tapering rather than stopping abruptly[2]		Patients requiring >1 CVC[3]	
		ADAMTS13 <10% (n=66)	ADAMTS13 ≥10% (n=222)	ADAMTS13 <10% (n=66)	ADAMTS13 ≥10% (n=222)	ADAMTS13 <10% (n=66)	ADAMTS13 ≥10% (n=222)
1	1996-1999	27.0 (2, 137)	8.5 (1, 54)	8/11 (73%)	21/54 (39%)	7/11 (64%)	13/54 (24%)
2	1999-2002	30.5 (3, 129)	7.0 (1, 183)	16/20 (80%)	11/53 (21%)	9/20 (45%)	10/53 (19%)
3	2002-2005	13.0 (1, 39)	6.0 (1, 45))	3/10 (30%)	10/47 (21%)	4/10 (40%)	10/47 (21%)
4	2005-2008	12.0 (5, 76)	6.0 (2, 21)	3/15 (47%)	2/27 (7%)	3/15 (20%)	3/27 (11%)
5	2008-2011	8.0 (6, 50)	6.0 (1, 31)	4/10 (40%)	1/41 (2%)	4/10 (40%)	4/41 (10%)
P		0.040	0.056	0.020	<0.001	0.044	0.027

[1]The days of PEX are defined as the number of days between the first and last PEX treatments. These data are a minimum estimate of the duration of central venous catheter exposure because the central venous catheter was not always removed on the day of the last PEX. The patient with 183 days of PEX in the 1999-2002 cohort was a boy with inherited complement Factor H deficiency.

[2]Tapering of PEX is defined as a schedule to skip days of treatment, with a gradual increase of the interval between PEX treatments until treatment is stopped. Stopping PEX abruptly is defined as daily PEX including the day of the last PEX.

[3]Most CVC replacements are elective procedures, for example to replace an initial femoral CVC with an internal jugular or subclavian vein CVC, when plasma exchange was required for longer than approximately one week, the time considered to be safe for a femoral CVC or to insert a new CVC when an exacerbation occurred after the initial CVC had been removed.

Table 6

Increasing use of corticosteroids and rituximab as adjuvant treatments for patients with TTP-HUS, 1996-2011

Cohort		Patients Treated with Corticosteroids (%)		Patients Treated with Rituximab (%)	
		ADAMTS13 <10% (n=66)	ADAMTS13 ≥10% (n=222)	ADAMTS13 <10% (n=66)	ADAMTS13 ≥10% (n=222)
1	1996-1999	6/11 (55%)	32/54 (59%)	0/11	0/54
2	1999-2002	11/20 (55%)	28/53 (53%)	0/20	0/53
3	2002-2005	8/10 (80%)	21/47 (45%)	1/10 (10%)	3/47 (6%)
4	2005-2008	15/15 (100%)	11/27 (41%)	5/15 (33%)	0/27
5	2008-2011	10/10 (100%)	28/41 (68%)	4/10 (40%)	9/41 (22%)
P		<0.001	0.777	<0.001	<0.001