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Posterior Reversible Encephalopathy Syndrome in Infection, Sepsis, and Shock

BACKGROUND AND PURPOSE: The cause of “posterior reversible encephalopathy syndrome” (PRES) is not established. We recently encountered several patients who developed PRES in the setting of severe infection. In this study, we comprehensively reviewed the clinical and imaging features in a large cohort of patients who developed PRES, with particular attention to those with isolated infection, sepsis, or shock (I/S/S).

METHODS: The clinical/imaging features of 106 patients who developed PRES were comprehensively evaluated. In 25 of these patients, PRES occurred in association with severe I/S/S separate from transplantation. The clinical/imaging features (computer tomography, MR imaging, and MR angiography [MRA]) of the patients with I/S/S were further evaluated, including organ/tissue/blood culture results, mean arterial blood pressure (MAP) at toxicity, extent of cerebral edema, and presence of vasospasm.

RESULTS: PRES occurred in association with I/S/S in 25 of 106 patients (23.6%), in addition to 4 other major clinical settings, including cyclosporine/FK-506 (post-transplant) neurotoxicity (46.2%), autoimmune disease (10.4%), postchemotherapy (3.7%), and eclampsia (10.4%). In the 25 patients with I/S/S, available cultures demonstrated a predominance of gram-positive organisms (84%). Blood pressure was “normal” at toxicity in 10 patients (MAP, 95 mm Hg); “severe” hypertension was present in 15 patients (MAP, 137 mm Hg). Extent of brain edema graded on imaging studies was greater in the normal MAP group compared with the severe hypertension group ($P < .05$). MRA demonstrated vasospasm in patients with severe hypertension and vessel “pruning” in the normal MAP group.

CONCLUSION: Infection/sepsis/shock may be an important cause of PRES, particularly in relation to infection with gram-positive organisms.

The imaging features of eclampsia and cyclosporine/FK-506 neurotoxicity seen after allogeneic bone marrow transplantation (allo-BMT) are similar. CT and MR imaging demonstrate cortex/white matter vasogenic edema in the parietal/occipital regions with less frequent frontal, temporal-occipital, and cerebellar involvement.¹⁻⁴ Isolated reports have demonstrated vasospasm at MR angiography (MRA) in both of these conditions.^{2,5-7} This imaging pattern has been identified in patients with systemic conditions, such as nonspecific renal inflammatory disease (glomerulonephritis, hepatorenal syndrome), systemic lupus erythematosus (SLE), Wegener granulomatosis, or postchemotherapy.⁸⁻¹⁵ The term “posterior reversible encephalopathy syndrome” (PRES) is commonly used in these patients focusing on the similarity in imaging appearance, in particular the common parietal/occipital distribution of the abnormality.¹²⁻¹⁵

We recently identified several patients who developed PRES in conjunction with severe infection or sepsis. The purpose of this study was to retrospectively evaluate the clinical conditions surrounding the development of PRES with particular attention to the frequency of association with infection, sepsis, or shock (I/S/S).

Materials and Methods

The radiology report data base at our institution was searched (Jan 1998–Aug 2005) for any patients where PRES or posterior reversible encephalopathy was cited in brain MR imaging reports. Further similar data base searches were performed for reference to cyclosporine neurotoxicity, tacrolimus/FK-506 neurotoxicity, SLE, Wegener granulomatosis, scleroderma (systemic sclerosis), hypertensive encephalopathy, preeclampsia, and eclampsia. Brain MR imaging studies along with CT imaging studies were reviewed in the identified patients for features consistent with the characteristics of cyclosporine/FK-506 neurotoxicity, eclampsia, or PRES.

Patients with imaging features consistent with PRES were tabulated combined with the PRES neurotoxicity data base belonging to one of the authors (Jan 1991–June 2002), and the resulting data were pooled. The combined data represent the spectrum of cases with PRES neurotoxicity for this report. Institutional Review Board approval was obtained for this retrospective study.

One hundred and six patients were identified who developed neurotoxicity and brain imaging consistent with the previous literature description of CsA/FK-506 neurotoxicity, eclampsia, or PRES. Criteria included complete or partial expression of the typical PRES pattern, complete or partial reversibility on follow-up imaging, or vasogenic edema as demonstrated by MR diffusion imaging. In 25 of these 106 patients, neurotoxicity and PRES developed in the setting of severe infection, sepsis, or shock. This report briefly reviews the clinical background of the 106 patients in the overall population and specifically focuses on clinical and imaging features encountered in the 25 patients with infection, sepsis, and shock.

Clinical Evaluation

The clinical inpatient and outpatient records of these patients were reviewed. Specific attention was paid to identify clinical features lead-

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ing up to and surrounding the development of PRES along with known associations including CsA/FK-506 neurotoxicity and eclampsia. The presence or absence of hypertension, CsA/FK-506 levels, evidence of endothelial injury and hemolysis (lactate dehydrogenase [LDH], platelet levels, red cell fragmentation [similar to BMT thrombotic microangiopathy]), evidence of immune system dysfunction (autoantibody formation, graft-versus-host effects, and organ rejection), liver function, renal function, pulmonary function, and presence of infection or sepsis were sought and tabulated. Where more than one clinical association was present, the dominant clinical association was used for tabulation.

In patients with infection, sepsis, and shock, evidence of coexistent “multiple organ dysfunction syndrome” (MODS) was sought and tabulated with guidance from the “sepsis-related organ failure assessment” (SOFA) score as developed by the European Society of Intensive Care Medicine 1994 consensus meeting.^{16,17} Parameters used by this score are designed to identify in a simple and concise fashion evidence of *developing* organ dysfunction/failure in the presence of sepsis including: coagulation, pulmonary, hepatic, renal, cardiovascular, and neurologic systems. Evidence of organ failure was sought in 4 of these systems (coagulation: drop in platelet count [$<150 \times 10^3/\text{mm}^3$]; pulmonary: respiratory failure or hypoxemia not related to pneumonia; liver: bilirubin elevation [$>1.2 \text{ mg/dL}$]; renal: creatinine elevation [$>1.2 \text{ mg/dL}$]) and tabulated. Neurologic dysfunction is intrinsically reflected in PRES neurotoxicity and cardiovascular dysfunction reflected in associated hypertension. Mean arterial pressure (MAP) at toxicity was calculated in a standard fashion ($\text{MAP} = 2/3 \text{ diastolic} + 1/3 \text{ systolic pressure}$).

Imaging Evaluation

CT was the sole imaging study in 18 patients with MR imaging available at toxicity in 88 patients (including comparison CT and follow-up MR imaging studies). CT studies were obtained with 5-mm section thickness through the posterior fossa along with 5–10-mm section thickness through the supratentorial hemispheres. Contrast material when used consisted of intravenous 150 mL iohalamate me-

glumine (Conray 60; Mallinckrodt, St. Louis, Mo) or iohexol 300 (GE Medical Products, Milwaukee, Wis).

MR imaging, where obtained, was performed at 1.5T including sagittal and axial T1-weighted images (TR/TE/section width/NEX, 600 ms/minimum/5 mm/1) with 5-mm section thickness and spin-echo or fast spin-echo axial proton attenuation (TR/TE/section width/NEX, 2000–2500/minimum/5 mm/1) and T2-weighted images (TR/TE/section width/NEX, 2500–3000/84–102effective/5/1). Contrast-enhanced T1-weighted images were obtained with 0.1 mmol/kg gadolinium dimeglumine (Magnevist; Berlex Laboratories, Wayne, NJ) or gadoteridol (Prohance; Bracco Diagnostics, Princeton, NJ) using typical T1-weighted parameters as described above. Fluid-attenuated inversion recovery (FLAIR) images (TR/TE/TI, 9000–10,000 ms/149 ms/2200 ms) and diffusion-weighted imaging (DWI; single-shot echo-planar; TR/TE/section width/matrix, 10,000 ms/minimum/5 mm/128) sequences were also available in most patients.

Imaging Features of CsA/FK-506 Neurotoxicity, Eclampsia, and PRES

The scope of features seen in CsA/FK-506 neurotoxicity, eclampsia, and the PRES imaging appearance has been described previously.^{1–4,9–15} The locations of the regions of imaging abnormality were itemized and tabulated. Specific regions were tabulated separately, including frontal lobe, parietal region, occipital lobe, temporal lobe, cerebellum, brain stem, basal ganglia, and deep white matter. Features of involvement were further characterized as patchy, confluent, or linear in appearance. The presence or absence of lesion enhancement was noted and tabulated. DWI features (normal/restricted) were identified. The presence of focal areas of brain infarction with restricted diffusion or regions of brain hemorrhage were itemized and tabulated.

Grading of Vasogenic Edema in PRES

In the patients with I/S/S, CT or MR imaging studies were graded for extent and severity of cortex and white matter vasogenic edema. Ex-

Table 1: Vasogenic edema scale

Edema Grade	Description	Points
Grade 1	Cortex edema, limited subcortical white matter edema or both Involved regions nonconfluent	1
Grade 2	Slight local cortex mass effect/distortion due to edema White matter edema slightly greater in thickness than cortex edema White matter edema extends into deep white matter Primarily without wide medial-to-lateral extension Some involved regions occasionally confluent	2
Grade 3	Local cortical mass effect/distortion due to edema White matter edema substantially greater in thickness than cortex edema Some limited and focal extension to ventricular surface Developing wide medial-to-lateral extension Involved regions partially confluent	3
Grade 4	Moderate local cortex mass effect/distortion due to the edema White matter edema substantially thicker than cortex edema Involved regions substantially extend to ventricular surface Diffuse wide medial-to-lateral extension Involved regions almost completely confluent	4
Grade 5	No ventricular distortion due to the edema White matter edema severe and dominates cortex edema Involved regions fully confluent and continuous Diffuse wide medial-to-lateral extension Fully extends to the ventricular surface Ventricular deformity due to the edema	5

Table 2: Categories and timing of PRES neurotoxicity

Toxicity Category	No. of Patients	Subgroup	No. of Patients	Time Point of PRES Relative to 'Association' Event				
				0–1 mos (# pts)	1–4 mos (# pts)	4–12 mos (# pts)	> 12 mos (# pts)	Not Known (# pts)
Cyclosporine/FK-506 toxicity	49	allo-BMT	26	16	5	4	1	
		SOT	20	5	3	5	7	
		CsA only	3					3
Postchemotherapy	4		4	3	1			
Infection/sepsis/shock	25	Infection/Sepsis	23	21	1			1
		Hemorrhagic Shock	2	2				
Eclampsia	11	Intrapartum	3					3
		Delayed	8	8				
Autoimmune	11		11					11
Miscellaneous	6		6					6
Total	106		106	56	10	9	8	23

Note:—# pts indicates number of patients; mos, months; SOT, solid organ transplant; CsA only, cyclosporine treatment in marrow diseases; PRES, posterior reversible encephalopathy syndrome; allo-BMT, allogenic bone marrow transplantation.

tent and severity of edema in the involved regions were independently assessed by 2 observers blinded to patients' blood pressure, studies were graded on a 5-point scale summarized in Table 1, and results were tabulated for each patient. Difference in patient grade was agreed upon by consensus. Edema grade results for patients with severe hypertension and without hypertension were separately averaged and compared.

Vascular Assessment

In 11 patients with I/S/S, MRA was available along with MR imaging in the time frame of neurotoxicity and PRES. MRA was obtained using 3D time-of-flight (TOF) technique (TR/TE/Flip angle/FOV/matrix/acquisitions, default/min/45°/18–22 cm/226 × 224/1) with multiple overlapping slab reconstruction. In 10 of 11 patients, MRA was obtained during initial MR assessment of neurotoxicity, and in 1 patient, MRA was obtained on a follow-up study 1 week after toxicity and after the patient had clinically stabilized.

MRA studies were evaluated for the presence or absence of vascular abnormality or vasospasm. Studies were blindly and independently graded by 2 neuroradiologists, and any differences were resolved by consensus. Traditional features of vasospasm or vasculitis were identified including: significant diffuse constriction of first-, second-, and third-order branch vessels, areas of focal vessel narrowing and constriction, and string-of-bead appearance.

Statistical Assessment

Statistical significance was evaluated using the SAS software package, PROCAPABILITY statistical analysis software function (SAS release 8.2; SAS Institute, Cary NC). Comparison between hypertensive and nonhypertensive subsets was performed with Student *t* test and Wilcoxon signed rank test. Statistical significance was considered to exist for $P < .05$.

Results

The clinical background of the 106 patients is summarized in Table 2. Seventy-two patients (67.9%) were female and 34 (32.1%) were male; their average age was 42.4 years (range, 17–79 years). Headache, vision change, altered mental status, nausea, or aphasia (alone or in combination) was the presenting symptom in 35 (33%) of patients and seizure (frequently accompanied by or preceded by headache or vision change) in 71 (67%). Blood pressure was normal (patient baseline) at

presentation in 32 patients, slightly elevated in 11 patients, and severe in 63 patients.

Overall Patient Clinical Profile

In 49 (46.2%) patients, neurotoxicity developed in association with cyclosporine/FK-506 immune suppression. Transplantation was present in 46 of 49 patients (solid organ, 20; allo-BMT, 26), and 3 patients received cyclosporine for treatment of marrow disease (pure red cell aplasia, aplastic anemia). Four (3.8%) patients developed PRES in association with cancer chemotherapy and in 11 (10.4%) patients, PRES occurred in association with autoimmune disease (SLE, 5 patients and 1 patient each with Wegener granulomatosis, scleroderma, polyarteritis nodosa, psoriasis, Graves disease, and rheumatoid factor positive arthropathy). PRES was associated with eclampsia or delayed eclampsia in 11 (10.4%) patients.

In 4 patients, PRES developed in association with increasing or acute hypertension with either chronic renal disease (nephrosclerosis; chronic renal failure and dialysis) or no obvious cause of acute hypertension (chronic drug use; prior renal cell carcinoma). In 2 patients, no specific cause was identified with known but unchanged chronic hypertension. In 25 (23.6%) of 106 patients, neurotoxicity and PRES were noted to occur in association with I/S/S.

PRES in Infection, Sepsis, and Shock

In 23 patients, significant infection and/or bacteremia occurred in close association with the development of PRES. In 2 additional patients, PRES developed after an episode of severe hemorrhagic shock. In 11 of the 23 patients with infection, clinical sepsis (sepsis, severe sepsis, or septic shock) was noted or suspected during their illness before development of PRES. The clinical profile and characteristics of the patients with infection, sepsis, and shock are summarized in Table 3.

In 21 of these 23 patients with infection, PRES developed immediately after or coincident with the severe infection or bacteremia. In 18 of these 21 patients, PRES occurred within 2 weeks of the infection and in 3 patients (1 each: abscess, wound infection, blast crisis with sepsis), neurotoxicity developed between 20 and 30 days of infection identification (overall average, 6.7 days; range, 0–30 days). In 19 of the 21 patients, organ or tissue infection was present, and in 2 patients, iso-

Table 3: Clinical features of patients with infection, sepsis, and shock

Pt #	Age	Sex	Major Clinical Problem and Infection	Cultured Organism		S/S	MOD	Delay	PRES Neurotoxicity	BP Base	BP Tox	MAP Tox
				Organ/Tissue	Blood							
Group 1												
1	39	M	Pneumonia with bronchial obstruction, decubitus ulcer	<i>S. aureus</i>	Staph coag neg	Y		13D	Headache Seizure	122/61	118/70	86
2	73	F	Gastric surgery, pneumonia, aspiration	<i>Pseudomonas</i>	<i>P. aeruginosa</i>	Y	CR	6D	Altered MS	157/77	128/80	78
3	59	F	Bowel perforation, abscess, sepsis, MOD, antihypertensive syndrome	Staph coag neg	Staph coag neg	Y	CP	13D	Altered MS	143/79	150/56	87
4	56	F	Thigh abscess	<i>Klebsiella</i>		Y	CP	27D	Seizure	156/68	164/75	104
5	24	F	CML in blast crisis, isolated bacteremia, sepsis, chemotherapy	<i>Enterococcus F1</i>	<i>Enterobacter</i>	Y	PL R	20D (15D)	Slurred speech Ataxia Seizure	122/82	125/85	98
6	20	M	ALL, chemotherapy, skin infection	Staph coag neg	1. Diphtheroids 2. Staph coag neg	-	CP LR	7D	Seizure	120/70	150/88	106
7	68	F	Necrotic pancreatitis, pancreatic abscess	Staph coag neg <i>Achromobacter</i>	Staph coag neg	Y	CP L	7D	Altered MS	141/67	168/68	101
8	55	F	Liver metastasis, open hepatic chemotherapy infusion, pneumonia	<i>S. aureus</i>	1. <i>S. pneumoniae</i> 2. Staph coag neg	Y	CP LR	3D	Altered MS	115/70	150/82	104
9	66	F	Toe infection and abscess, diabetic	<i>S. aureus</i> Staph coag neg Yeast			R	9D	Seizure	132/52	160/60	93
10	79	F	Lap-cholecystectomy; severe abdominal hemorrhage			Y	CP LR	7D	Altered MS	138/73	137/74	95
Group 2												
11	61	F	Postoperative wound infection	<i>S. aureus</i>	<i>S. aureus</i>			11D	Headache Vision loss	145/65	210/102	138
12	24	F	Isolated bacteremia 2 mo post Tx removal		<i>S. viridans</i>		R	0D	Headache Seizure	125/90	170/126	140
13	22	M	Original sickle cell crisis w/pneumonia-bacteremia, new sickle cell crisis w/heavy rectal colonization	N/A <i>Enterococcus F2</i>	Staph coag neg		CR	2M	Sickle crisis Seizure	122/80	200/100	133
14	37	M	Chronic septic arthritis, shoulder abscess	<i>S. aureus</i>	N/A		CR	?	Headache Vision change Seizure	175/85	184/111	135
15	26	F	Crohn disease, bowel perforation, pneumonia, abdominal abscess	<i>Enterococcus F1</i> <i>Enterococcus F2</i> <i>E. coli</i>	Staph coag neg	Y	CP	7D	Seizure	115/65	182/100	126
16	51	F	Breast carcinoma, auto-BMT, pneumonia	<i>Pseudomonas</i> <i>Klebsiella</i> Staph coag neg	1. <i>Micrococcus</i> 2. <i>Enterococcus</i> 3. Staph coag neg	Y	C p L	9D	Seizures	121/74	164/100	123
17	55	M	Foot infection, diabetic	N/A on antibiotics			C	0D	Headache Vision change	191/88	215/115	148
18	57	F	Post gastric stapling, acute UTI	<i>Enterococcus F1</i>	Staph coag neg			2D	Altered MS Seizure	136/70	203/93	129
19	54	F	Pneumonia, severe, intubated	N/A outside hosp				9D	Vision change Altered MS	112/85	200/100	133
20	81	F	Axillary abscess, chemotherapy	<i>S. aureus</i>	1. <i>S. aureus</i> 2. Staph coag neg	Y	CL	30D	Slurred speech Altered MS Seizure	130/52	203/110	141
21	37	F	Necrotizing pancreatitis, pneumonia	N/A outside hosp				7D	Headache Seizure	162/92	220/126	157
22	56	F	Sickle cell crisis, pneumonia	<i>S. viridans</i>			R	4D	Altered MS Seizure	150/84	170/110	130
23	24	F	Alcohol intoxication, shock, bowel perforation	N/A on antibiotics		Y	CP LR	6D	Seizure	140/90	203/113	143
24	38	F	Peritonitis, PD, renal insufficiency	<i>Pseudomonas</i>	<i>Pseudomonas</i>	Y	CP R	14D	Altered MS	145/94	210/110	143
25	19	F	Dialysis catheter hemorrhage					15D	Headache Vision change Seizure	149/86	207/106	140

Note:—S/S indicates clinically hemorrhagic, shock or sepsis, severe sepsis, or septic shock before developing PRES; Y, yes; MOD, multiorgan dysfunction developed coincident with PRES; C, coagulation; drop in platelet count; P, pulmonary dysfunction—edema, intubation; L, hepatic dysfunction, rising and elevated bilirubin; R, renal dysfunction, rising and elevated creatinine; Delay, closest time from recognized infection/bacteremia/shock to onset of neurotoxicity and PRES; MS, mental status; BP, blood pressure (mm Hg); base, baseline; tox, at toxicity; MAP, mean arterial pressure; N/A, not available; Tx, transplant; PD, peritoneal dialysis; UTI, urinary tract infection; PRES, posterior reversible encephalopathy syndrome; CML, chronic myelogenous leukemia; ALL, acute lymphoblastic leukemia; auto-BMT, auto-bone marrow transplant; *S. aureus*, *Staphylococcus aureus*; Staph coag neg, coagulase-negative Staphylococci; *E. coli*, *Escherichia coli*; *S. viridans*, *Streptococci viridans*; *S. pneumoniae*, *Streptococci pneumoniae*. Multiple organisms listed together correspond to mixed flora infections. Numbered blood culture organisms correspond to separate blood culture results with different organisms in the PRES time frame. F1, faecalis; F2, faecium. In patient 5, initial neurotoxicity began 15 days after sepsis/7 days after chemotherapy. Initial imaging negative (16 days), repeat imaging demonstrating PRESS (20 days).

lated bacteremia and sepsis occurred. Of the 19 patients with organ/tissue infection, 12 patients also demonstrated bacteremia coincident with the PRES event. In 4 of the 19 patients with organ/tissue infection, documented infection was present but primary site cultures were not available due to ongoing antibiotic treatment. In 2 of the 23 patients with infection, timing was difficult to assess because of disease chronicity (1 patient with diabetes, chronic septic arthritis [*Streptococcus aureus*] requiring frequent debridement and multiple prior episodes of bacteremia developed neurotoxicity during renal dialysis; 1 patient with sickle cell disease where PRES occurred with high white count, repeat sickle cell crisis, and heavy rectal enterococcal colonization but 10 weeks after pneumonia with documented bacteremia). Four of 23 patients with infection/sepsis also received chemotherapy.

Organ or Tissue Infection

Organ/tissue culture results were available in 16 of 23 patients (15 of 21 patients coincident with PRES; 1 patient with chronic septic arthritis). These are reviewed in Table 3. In 10 infections, a single organism was isolated, and in 6 infections, mixed flora was present. In single-organism infections, gram-positive cocci were present in 8 of 10 and where mixed flora was cultured, at least one of the organisms was gram-positive. Gram-positive cocci were isolated, therefore, in 14 of 16 primary site infections.

Blood Cultures and Septicemia

Blood cultures were positive in 14 of the 21 patients, where infection was coincident with PRES (2 with primary bacteremia/sepsis, 12 with organ or tissue infection) as well as the 1 patient with sickle cell disease, sickle cell crisis, and pneumonia. The results are summarized in Table 3. In 10 patients, a single blood culture was positive coincident with PRES, and in 4 patients, multiple blood cultures were positive coincident with toxicity. Similar to the results of tissue and organ infection, most organisms identified (12 of 15) were gram-positive cocci.

Multiple Organ Dysfunction Accompanying I/S/S and PRES

In 18 of the 25 patients with I/S/S, evidence of evolving multiple organ dysfunction was identified coincident with the development of neurotoxicity/PRES. New or worsening organ dysfunction was documented in the systems typically involved in MODS including: coagulation dysfunction with platelet consumption (14 patients), pulmonary dysfunction separate from pneumonia (11 patients), liver dysfunction (9 patients), and renal dysfunction (12 patients). Two or more systems were abnormal and changing coincident with PRES in 15 patients (4-system dysfunction: 5 patients; 3-system dysfunction: 4 patients; 2-system dysfunction: 6 patients) with single-system dysfunction noted in 3 patients.

In 5 of 15 patients, manual peripheral smears were available at the time of toxicity and were abnormal demonstrating red cell fragmentation. In 8 of 9 patients, LDH levels obtained at toxicity were elevated and in 3 of these patients, peripheral smears were available and demonstrated red cell fragmentation consistent with hemolysis. In 7 of the 8 patients with elevated LDH, a significant decline in platelet count was also

noted suggesting a consumptive coagulopathy and endothelial injury.

Blood Pressure

Average baseline blood pressures and blood pressure at the time of toxicity are listed in Table 3. Two separate groups of patients were identified. Group 1 (referred to as “normotensive”): In 10 patients (40%), blood pressure was either normal/patient’s baseline at toxicity (6 patients) or demonstrated only mild systolic pressure elevation relative to patient baseline at toxicity (4 patients). Group 2 (referred to as “severe hypertensive”): In 15 patients (60%), severe hypertension was present with significant elevation of systolic pressure (>200 mm Hg), diastolic pressure (>100 mm Hg), or both. MAP at toxicity in group 1 was 95 mm Hg (range, 78–106 mm Hg) and MAP at toxicity in group 2 was 137 mm Hg (range, 123–157 mm Hg).

Imaging Features

The imaging features of patients who developed neurotoxicity/PRES coincident with I/S/S are reviewed in Tables 4 and 5 and Figs 1–6. Patients demonstrated regions of vasogenic edema in typical locations reported for PRES, including cerebellum, temporal lobes, occipital region, parietal region, and frontal lobes. Unusual lesion locations were noted in 6 patients, including brain stem (medulla, pons, or midbrain), thalamus, and caudate nucleus. In 17 patients, DWI was available at 1 of the initial imaging evaluations. DWI was normal without restricted diffusion in 15 of 17 studies with 2 patients demonstrating areas of focal restricted diffusion along with focal areas of hemorrhage.

Follow-up imaging in 18 patients demonstrated reversal (12 patients) or partial/substantial reversal (6 patients) of the PRES imaging appearance. In 5 patients, follow-up imaging was not performed but the patients’ symptoms (altered mentation, headache, vision change) resolved completely. Two patients died of sepsis-related complications before repeat imaging was obtained.

Vasogenic Edema

Extent of brain edema was compared between patients from groups 1 and 2, and the results are summarized in Table 4. Vasogenic edema was judged greater in the “normotensive” patients (group 1: average 3.3) with less edema present in the “severely hypertensive” patients (group 2: average 2.07). This difference was statistically significant (Student *t* test: $P = .01$; Wilcoxon score: $P = .03$). Patients in group 1 demonstrated a greater range in the degree of brain edema; 4 of 11 (36%) demonstrated grade 4 or 5 edema (Figs 1–5). In contrast, patients in group 2 generally demonstrated either a mild or a moderate degree of vasogenic edema.

Vascular Features

MRA was available at the initial MR assessment of neurotoxicity in 10 of 25 patients with infection, sepsis, or shock (group 2 severe hypertension at toxicity: 6 patients; group 1 normotensive at toxicity: 4 patients). All 6 patients in group 2 demonstrated vessel irregularity at toxicity consistent with vasospasm (Fig 6). In 2 patients, initial MRA at toxicity

Table 4: Imaging features in patients with infection, sepsis, and shock

Pt #	Imaging Locations of PRES Vasogenic Edema						MRA	Imaging Modality	DWI	F/U Imaging	Clinical at Discharge	Edema Grade	MAP
	C	T	O	P	F	Misc							
Group 1													
1			x	x	x			MR	n/o		Resolved	3	86
2							Spasm-imp	MR	Neg	Res		2	78
3		x	x	x	x			MR	Neg	Resolving	Resolved	5	87
4	x	x	x	x	x	t	Pruning	MR	n/o		Resolved	5	104
5		x	x	x	x			CT		Res		3	98
6				x				CT			Expired	2	106
7							Pruning	MR	Neg	Resolving	Resolved	2	101
8		x	x	x	x			CT		Res		5	104
9	x		x	x	x		Normal	MR	Neg	Res		2	93
10			x	x	x			MR	Neg*	Resolving	Resolved	4	85
Group 2													
11	x	x	x	x		t mb	Spasm/prun	MR	Neg		Normal	2	138
12	x		x	x	x			MR	Neg	Res		3	140
13	x	x	x	x	x	bs mb c		MR	Neg	Res		1	133
14	x	x	x	x	x	bs		MR	Neg	Res		3	135
15		x	x	x	x			CT			Resolved	1	126
16		x	x	x				CT			Expired	2	123
17	x		x	x		t	Spasm	MR	Neg	Resolving	Resolved	2	148
18		x	x	x	x		Spasm	MR	Neg	Resolving	Resolved	3	129
19			x	x	x		Spasm-rev	MR	Neg	Res		1	133
20	x	x	x	x		bs		MR	Neg	Resolving	Resolved	2	141
21				x	x			MR	Neg	—	Resolved	1	157
22		x	x	x	x		Spasm	MR	Neg	Res		4	130
23	x	x	x	x				MR	Neg	Res		1	143
24	x	x	x	x			Spasm-rev	MR	Neg*	Res*		3	143
25		x	x	x	x			MR	n/o	Res		2	140

Note:—PRES indicates posterior reversible encephalopathy syndrome; C, cerebellum; T, temporal lobe/inferior temporal-occipital junction; O, occipital lobe; P, parietal region; F, frontal lobes; bs, brain stem including medulla and pons; mb, midbrain; t, thalamus; c, caudate nucleus; rev, spasm reverses; imp, spasm improves; spasm/prun, middle cerebral artery spasm with posterior cerebral artery pruning; DWI, diffusion-weighted image characteristics; n/o, DWI not obtained with MR imaging study; Neg, no evidence of restricted diffusion to suggest cytotoxic edema; Neg*, no restricted diffusion in the majority of vasogenic edema with focal region of restricted diffusion and hemorrhage noted; Res, vasogenic edema completely resolved on follow-up imaging studies; Res*, vasogenic edema resolved with minor persistent abnormal signal in region of previously noted restricted diffusion, infarction, or focal hemorrhage; Resolving, resolving vasogenic edema on follow-up imaging studies or resolving clinical symptoms related to PRES; Resolved, clinical symptoms at PRES neurotoxicity resolved; MAP, mean arterial pressure.

Table 5: Vasogenic edema grade in Group 1 (Normotensive) and Group 2 (Severely Hypertensive) Patients

Blood Pressure Group	Vasogenic Edema Grade (Number of Patients)					Group Average
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	
Group 1	0	4	2	1	3	3.3
Group 2	5	5	4	1	0	2.07

demonstrated vasospasm, and follow-up MRA demonstrated reversal of spasm with vessel caliber and shape normalization.

In the patients in group 1 (normotensive), MRA at toxicity demonstrated vessel “pruning” with reduced second- and third-order branch visualization in 2 patients and vessel pruning with reversible spasm on follow-up MRA (Fig 5) in 1 patient. In 1 normotensive patient, MRA appeared normal.

Discussion

The imaging findings of “PRES” and associated neurotoxicity are recognized.¹⁻¹⁵ This imaging pattern is typically seen in patients who develop eclampsia or cyclosporine/FK-506 neurotoxicity after transplantation, but other associations have been reported, including autoimmune disease (such as SLE or Wegener granulomatosis) and hypertension. These patients typically present with several days of headache progressing to

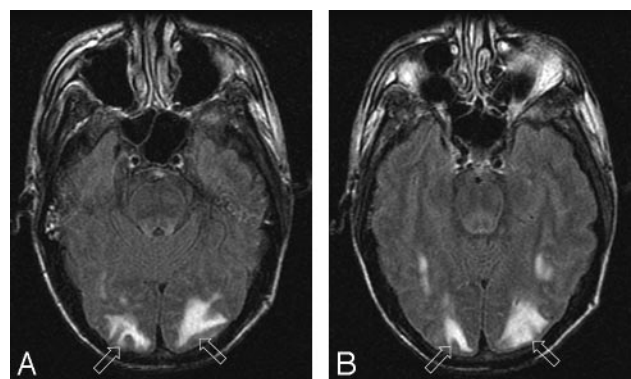


Fig 1. Patient 1 is a 39-year-old man with baseline blood pressure 122/61 mm Hg who had severe pneumonia with bronchial obstruction. Bronchial lavage grew *Staphylococcus aureus* and blood culture grew coagulase-negative staphylococci. Neurotoxicity developed 13 days after positive cultures with severe headache followed by a seizure with blood pressure at toxicity 118/70 mm Hg.

A–B, Brain MR imaging (FLAIR sequence) demonstrates moderate signal intensity abnormality from vasogenic edema in the occipital lobes bilaterally (open arrows) typical of the PRES pattern with full extension to the ventricular surface and moderate local cortical mass effect judged grade 3. Follow up imaging was not obtained, but the patient’s symptoms resolved completely.

visual disturbance and/or grand mal seizure.¹⁸ Unstable blood pressure frequently accompanies toxicity, but significant hypertension may be absent (25%–30% of patients).^{2,19}

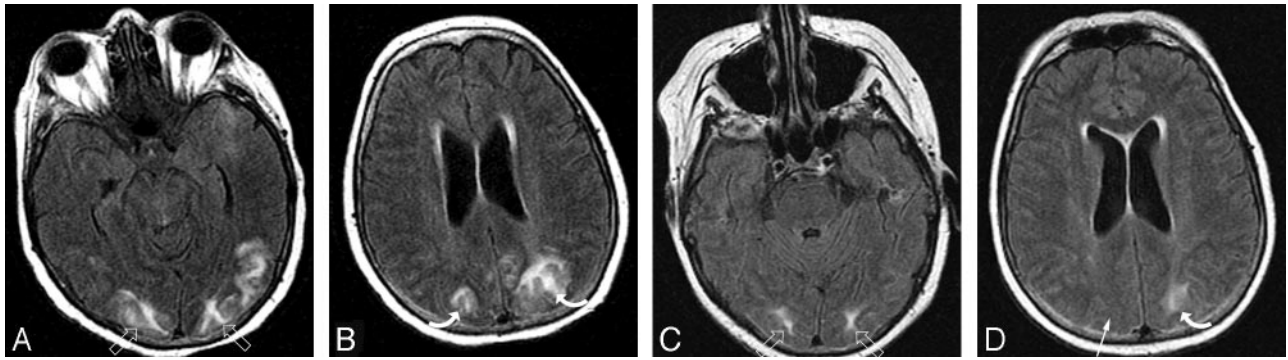


Fig 2. Patient 7 is a 68-year-old woman with necrotic pancreatitis, a pancreatic abscess, and baseline blood pressure of 141/67 mm Hg. Abscess grew mixed flora with coagulase-negative staphylococci and *Acinetobacter baumannii* and blood culture was positive for coagulase-negative staphylococci. Altered mental status with PRES developed 7 days after positive cultures with blood pressure at toxicity of 168/68 mm Hg.

A-B, Brain MR imaging (FLAIR sequence) demonstrates vasogenic edema in the occipital (*open arrows*) and parietal region (*curved arrows*) bilaterally typical of PRES with extension into the deep white matter but no extension to the ventricle surface judged grade 2.

C-D, Brain MR imaging (FLAIR sequence) obtained 1 month after initial imaging and toxicity demonstrates near complete resolution of the edema in the occipital (*open arrows*) and left parietal region (*curved arrow*) with complete resolution in the right parietal area (*arrow*).

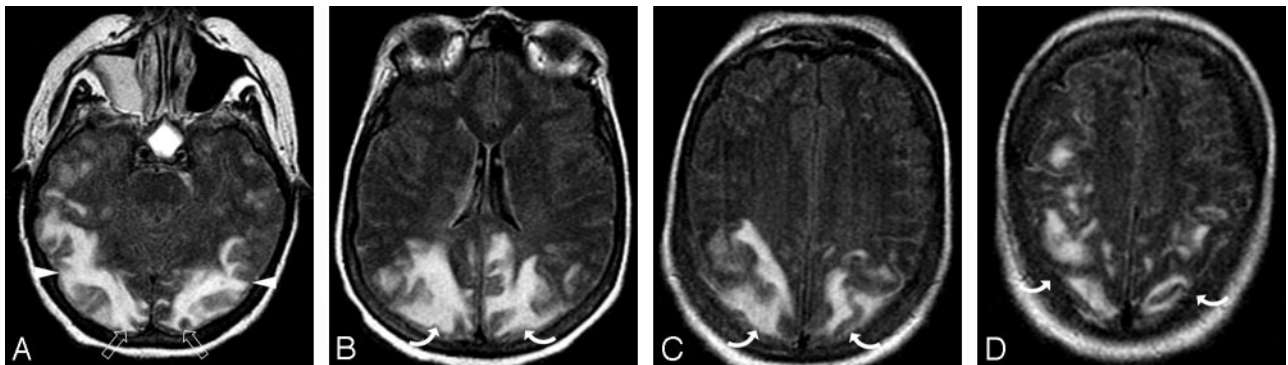


Fig 3. Patient 4 is a 56-year-old woman with a baseline blood pressure of 156/68 who developed a thigh abscess with culture growing mixed flora (*Klebsiella pneumoniae* and enterococci). She developed MOD (coagulopathy, acute respiratory distress syndrome, acute renal failure, liver failure, and shock liver). On day 27 of intensive treatment of her infection and multiorgan failure, the patient developed altered mentation followed by a generalized seizure and blood pressure of 164/75 mm Hg.

A-D, Brain MR imaging (FLAIR sequence) obtained the 1-day after neurotoxicity demonstrates severe and extensive vasogenic edema primarily involving the subcortical white matter of the parietal (*curved arrows*), occipital (*open arrows*), and temporal lobe regions (*arrowheads*) bilaterally with ventricular distortion from edema judged grade 5.

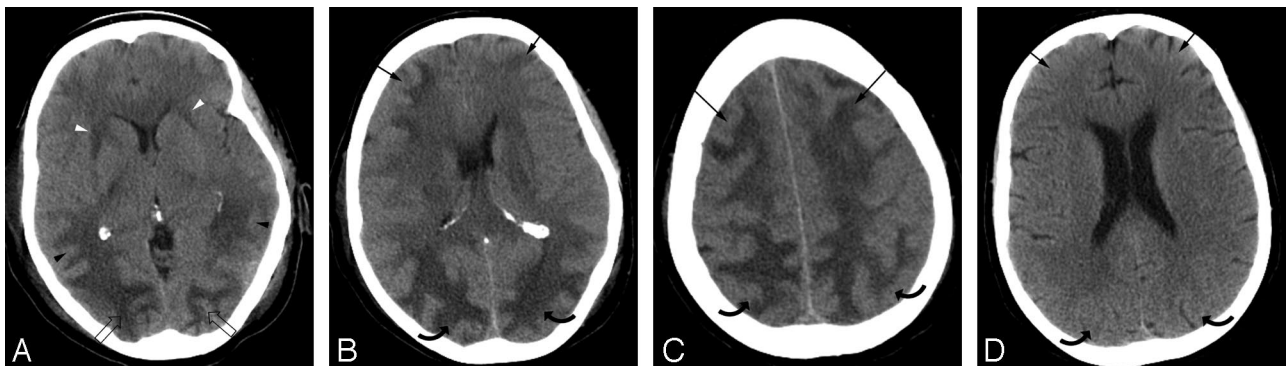


Fig 4. Patient 8 is a 55-year-old woman with multiple liver metastases from renal cell carcinoma who underwent liver wedge resection and intraoperative chemotherapy infusion. Baseline blood pressure was 115/70 mm Hg. She developed ARDS and *Streptococcus pneumoniae* sepsis 3 days after resection followed by pneumonia (*S aureus*) and line sepsis (coagulase-negative staphylococci). Patient developed altered mental status 3 days after pneumonia and bacteremia with blood pressure at toxicity of 150/80 mm Hg.

A-C, Brain CT images obtained at toxicity demonstrate vasogenic extensive edema in the occipital (*open arrows*), parietal (*curved arrows*), and frontal regions (*arrows*) bilaterally with focal edema also noted in the anterior limb internal capsule bilaterally (*arrowheads*) consistent with PRES with ventricular compression and deformity from the edema judged grade 5.

D, Follow-up brain CT imaging performed 1 month after initial imaging demonstrates complete reversal of the PRES pattern shown here in the parietal (*curved arrows*) and frontal (*arrows*) regions bilaterally.

The cause of PRES is controversial and unproven. Neurotoxicity and PRES are associated with eclampsia, cyclosporine/FK-506 toxicity (typically after allo-BMT or solid organ transplantation), and systemic chemotherapy.¹⁻¹¹ PRES is also seen

in patients with autoimmune disease, medical-renal disease, and severe hypertension.¹²⁻¹⁵ Isolated studies have suggested an association with hypomagnesemia, hypercholesterolemia, and human leukocyte antigen mismatch in allo-BMT.²⁰

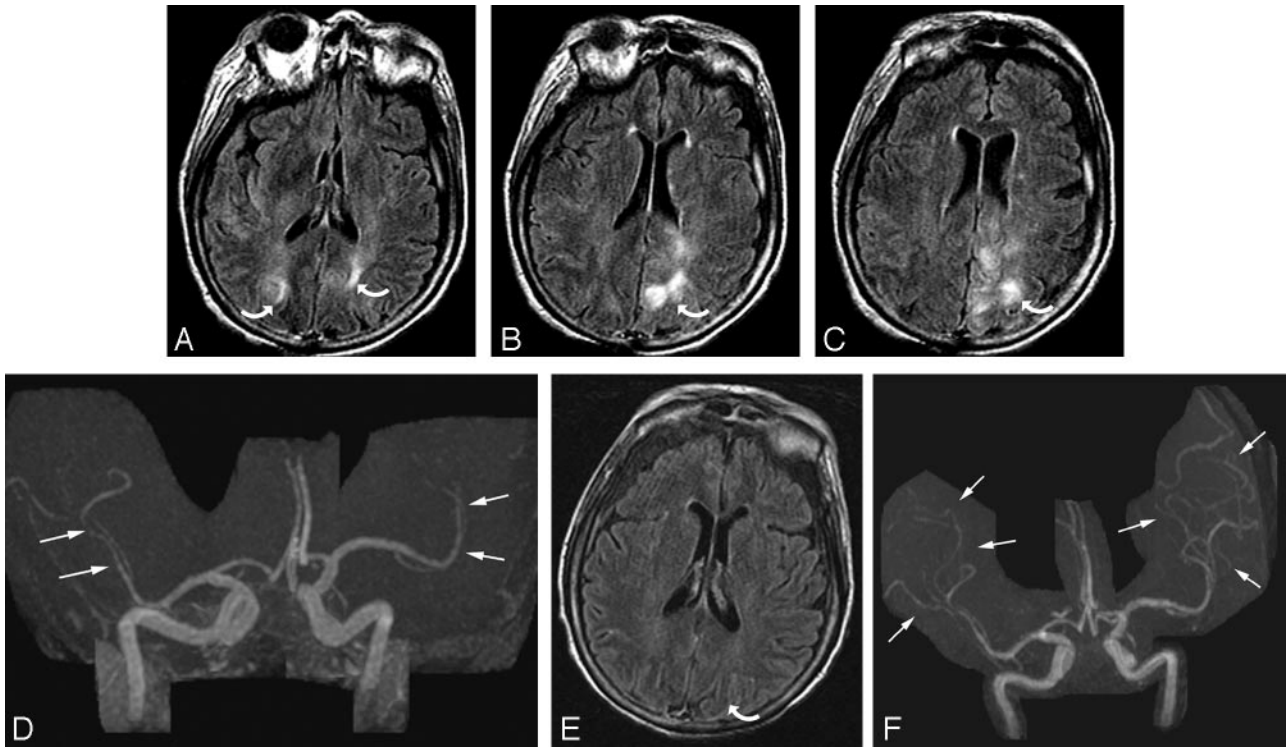


Fig 5. Patient 2 was a 73-year-old woman who had undergone gastric surgery. Her baseline blood pressure of 157/77 mm Hg. She developed aspiration and pneumonia. Bronchial washings and blood cultures grew *Pseudomonas aeruginosa*. Neurotoxicity developed 6 days after positive cultures with altered mental status and blood pressure 128/80 mm Hg. A-C, Brain MR imaging (FLAIR sequence) obtained at the time of toxicity demonstrates an unusual pattern of vasogenic edema in the parietal region bilaterally much greater on the left (curved arrows) involving both cortex and some extension to the deep white matter judged grade 2. D, MRA obtained at the same time as imaging demonstrates diminutive severely "pruned" intracranial vessels, in particular MCA branches (arrows). E, Follow-up brain MR imaging (FLAIR sequence) obtained 1 month after initial imaging demonstrates complete resolution of the vasogenic edema bilaterally shown here only on the left (curved arrow). Incidental subdural hygromas are also present. F, Follow-up MRA also obtained 1 month after initial imaging demonstrates marked improvement in vessel visualization with partial reversal of the severe "pruning" and spasm in the MCA branches (arrows) bilaterally. The patient's mental status completely normalized.

Potential biologic mechanisms for development of PRES have included factors that induce endothelial injury, such as the immune suppressive drugs cyclosporine and FK-506, endothelial activation/injury in eclampsia, endothelial injury from pretransplantation conditioning regimens, or graft-versus-host effects.^{2,21,22} Hypertension with forced hyperperfusion has also remained popular.^{3,23,24}

Our results demonstrate 4 important observations in PRES including: (1) association with infection/sepsis/shock, (2) association with gram-positive organisms, (3) inverse effect of severe hypertension on the extent of vasogenic edema, and (4) high frequency of associated cerebral vasospasm.

PRES and Its Association with Infection, Sepsis, and Shock

The first unexpected observation in our study is that PRES seemed to occur in patients with infection, sepsis, and shock. In 18 of 25 patients, PRES occurred within 2 weeks of bacteremia or organ/tissue infection (abscess, pneumonia, wound infection), and in 3 patients, PRES developed within 30 days of abscess drainage or bacteremia. In 2 additional patients, neurotoxicity occurred within 2 weeks of severe hemorrhagic shock. If one eliminates patients with transplantation or eclampsia, significant infection, sepsis, or shock was present in 25 of 49 patients (51%) in the overall study group. We believe

this is the first report to suggest that PRES may be associated with severe infection, sepsis, or shock.

Response to infection is an extremely complex process. At the fundamental biologic level, several systemic events occur simultaneously, including anti-infective, acute inflammatory, metabolic, pro-coagulant, and thermoregulatory changes.^{17,25-28} When infection is present, the role of the immune system is to 1) contain the infection, 2) target or traffic the inflammatory response to the infected region, and 3) prevent the inflammatory response from becoming systemic.¹⁷ If infection becomes overwhelming or if the immune response is inadequate, a septic clinical state can develop. The septic response to infection is known to occur without or with bacteremia (demonstrating identical morbidity and mortality), and cell-wall antigens of the infective organisms (endotoxin, exotoxin) are considered likely mediators.^{17,25-28} Both endotoxin (lipopolysaccharide [LPS] from gram-negative cell wall) and exotoxins/enterotoxins (peptidoglycan and lipoteichoic acid from gram-positive cell wall) are well known to be powerful stimulants of systemic inflammatory response, leukocytes, and endothelial interaction.^{17,28} It is noteworthy that no obvious source of infection can be identified in 30%–50% of cases that demonstrate a septic clinical presentation.¹⁷

Endothelial activation/injury is considered central to the development of the primary infection and secondary septic

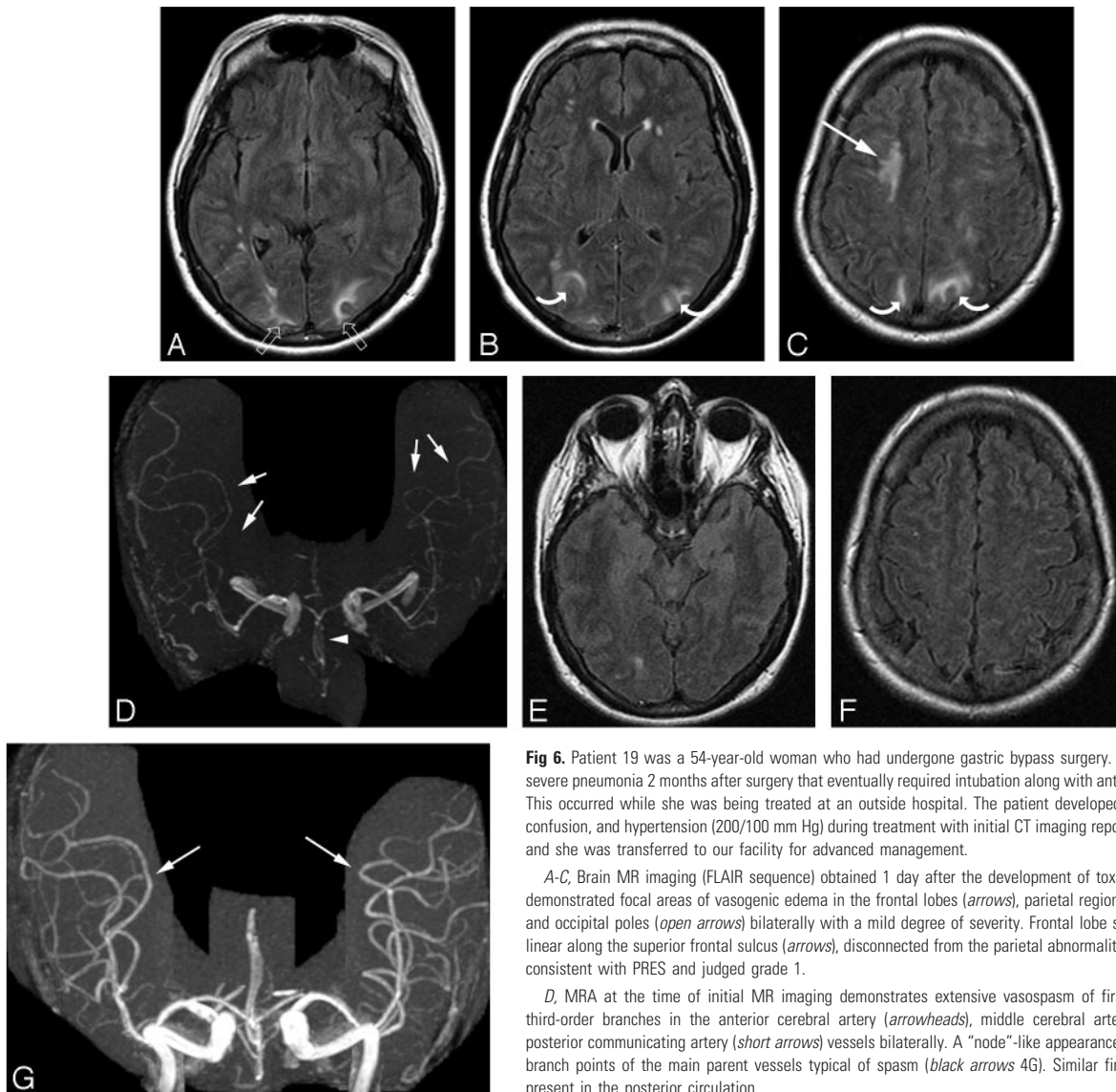


Fig 6. Patient 19 was a 54-year-old woman who had undergone gastric bypass surgery. She developed a severe pneumonia 2 months after surgery that eventually required intubation along with antibiotic treatment. This occurred while she was being treated at an outside hospital. The patient developed vision changes, confusion, and hypertension (200/100 mm Hg) during treatment with initial CT imaging reported as negative, and she was transferred to our facility for advanced management.

A-C, Brain MR imaging (FLAIR sequence) obtained 1 day after the development of toxicity and transfer demonstrated focal areas of vasogenic edema in the frontal lobes (arrows), parietal region (curved arrows), and occipital poles (open arrows) bilaterally with a mild degree of severity. Frontal lobe signal intensity is linear along the superior frontal sulcus (arrows), disconnected from the parietal abnormality (curved arrows) consistent with PRES and judged grade 1.

D, MRA at the time of initial MR imaging demonstrates extensive vasospasm of first-, second-, and third-order branches in the anterior cerebral artery (arrowheads), middle cerebral artery (arrows), and posterior communicating artery (short arrows) vessels bilaterally. A "node"-like appearance is seen at many branch points of the main parent vessels typical of spasm (black arrows 4G). Similar findings were also present in the posterior circulation.

E-F, Axial FLAIR image obtained on follow-up imaging study 11 days after the initial study demonstrates reversal of the vasogenic edema in all regions.

G, Repeat MRA obtained 11 days after the initial study demonstrates resolution of the extensive vasospasm with a near-normal appearance of all vessels (arrows).

response.^{17,29-32} This process (which is mediated by inflammatory cytokine release [tumor necrosis factor (TNF) α , interleukin (IL)-1 β , and other cytokines]) leads to up-regulation of endothelial surface antigens (P-selectin, E-selectin, ICAM-1) with increased white cell adherence, microcirculatory dysfunction, and altered vascular tone, vascular permeability, and coagulation.^{17,28,31,33,34} Microcirculatory dysfunction develops in part because of leukocyte adherence/trafficking with reduced local tissue blood flow at the capillary/venule level.³⁴ An alteration in vascular tone develops secondary to competing vasoconstrictive (platelet degranulation with thromboxane release, endothelin-1, angiotensin, vasopressin, and central sympathetic stimulation) and vasodilatory (nitric oxide, prostacyclin) effects.^{17,33} Significant vascular instability has been documented in 50% of septic patients within 28 days of the infection.²⁶

The potent vasoconstrictor endothelin-1 is released at its highest levels in sepsis, and morbidity/mortality in sepsis has been shown to parallel plasma endothelin-1 concentra-

tion.³⁵⁻³⁷ The inflammatory cytokines TNF- α and IL-1 up-regulate endothelin-1 mRNA production and stimulate its release from endothelial cells.³⁸⁻⁴⁰ Endotoxin also promotes the release of endothelin.⁴¹ Perhaps intermittent episodes of hypertension occur in sepsis but are difficult to recognize because of confounding factors (pain, intubation) and simple management with antihypertensive agents.

The clinical features of our patients parallel the general observations on sepsis with: 1) primary infection most commonly in the lungs, abdomen, wound or urinary tract, 2) blood culture-positive and blood culture-negative cases identified and 3) vascular instability and PRES developing within 14–30 days of severe infection. Endothelin-1 could contribute to the development of PRES in I/S/S.

Multiple Organ Dysfunction

The decision to group the patients with infection, sepsis, and hemorrhagic shock together is not arbitrary or for mere convenience. It is recognized that the systemic effects

present in these conditions are similar and that a final common course/end point can occur with multiple organ system dysfunction and/or failure (MODS) including: coagulation, pulmonary, hepatic, renal, cardiovascular, and neurologic.^{30,42-44} This response to I/S/S seems to represent the effects of systemic toxicity similar to the recently described "Systemic Inflammatory Response Syndrome" (SIRS) or MODS.^{27,42-47} Cytokine response (TNF- α , IL-1) is believed to play a critical role in the development of this effect.^{42-45,48}

In 18 of our patients with I/S/S, additional multiple organ system dysfunction (separate from neurologic and cardiovascular) was identified coincident with neurotoxicity and PRES similar to patterns observed in patients with MODS.

Gram-Positive Sepsis

The second important observation in these patients is the unexpectedly high incidence of gram-positive infection. In 16 of 19 culture-positive patients (84%), gram-positive organisms were identified in the primary infection site, blood cultures, or both. Gram-positive organisms are becoming more frequently identified in association with bacteremia and sepsis from both community-acquired and nosocomial sources with *Staphylococcus aureus*, coagulase-negative staphylococci, and enterococci accounting for 30%–50% of cases.⁴⁹⁻⁵¹

The mechanisms involved in gram-positive sepsis are different from gram-negative sepsis with cell surface antigen (exotoxins: peptidoglycan and lipoteichoic acid) and superantigen-related T-cell stimulation of cytokine release compared with the more limited traditional T cell trigger of inflammation/cytokines as occurs with endotoxin/LPS from gram-negative organisms.^{17,52-56} Superantigens demonstrate a markedly greater interaction rate with the overall T cell population (5%–20% of T cells for superantigens versus 1 in 10⁴–10⁶ T cells for traditional antigen) with broader T cell stimulation and cytokine response.^{17,52} This broader, more generalized response to gram-positive organisms could underlie the onset and systemic manifestations in patients with PRES.

Although our study was not designed to assess the incidence of PRES in infection/sepsis/shock, an approximate reference point can be drawn from the predicted incidence of septic shock in patients with sepsis. The incidence of sepsis in the United States is estimated to be approximately 240 patients/100,000 persons per year; septic shock is estimated to occur in approximately 7%–8%.^{27,57} For our region, this would translate into 330 to 380 cases of septic shock per year distributed among 20 hospitals (approximately 115–190 gram-positive; 5.7–10 cases per year). The number of patients we identify with infection/sepsis and PRES (approximately 2.5–3 patients per year) is similar to the incidence of gram-positive septic shock for a single institution in our geographic region (excluding transplantation).^{27,58} It is interesting that acute graft-versus-host disease (GVHD) seen after allo-BMT has been labeled a "distortion of the cellular response" to infection.⁵⁷

PRES Imaging Appearance, MRA, and Hypertension

The third crucial and unexpected observation in our patients with I/S/S is that the extent of brain edema graded on imaging studies appears to be inversely related to blood pressure at

toxicity. Normotensive patients (average MAP, 95 mm Hg) demonstrated the *greatest* degree of vasogenic edema, whereas severely hypertensive patients (average MAP, 137 mm Hg) demonstrated less brain edema, and this difference is statistically significant ($P < .05$). Fourth, in those patients for whom MRA was available, clear evidence of vasospasm or vessel "pruning" was observed. In the patients with severe hypertension, typical features of vasospasm were present and reversible where follow-up MRA was available for comparison. In normotensive patients, a combination of second- and third-order vessel "pruning" were noted. The reason behind these observations is not certain.

Although hypertension is frequently cited as the *cause* of PRES, blood pressure is not elevated in all cases. In 20%–30% of patients with cyclosporine toxicity or eclampsia, blood pressure is normal at toxicity.^{2,19} In preeclampsia/eclampsia, hypertension develops secondary to and along with complex systemic interactions, including endothelial activation/injury, platelet consumption, hemolysis, resultant vasospasm and vascular constriction, endothelial leakage, and organ hypoperfusion.⁵⁹⁻⁶¹ Similar systemic effects are also present in other conditions, including transplantation and autoimmune disease.^{57,62-78} These issues suggest that a mechanism other than hypertension could be responsible for PRES.

Vessel "pruning" in our normotensive patients could reflect slow or sluggish cerebral blood flow, perhaps related to microcirculatory effects, such as enhanced platelet/white cell adherence/trafficking at the capillary/venular level.^{29,34} The effects of microcirculatory abnormality might be demonstrated by a flow-sensitive technique such as MR perfusion.

In the "severely" hypertensive patients, recognizable vasospasm could reflect involvement of larger cerebral vessels in the "vasculopathy" process. Alternatively, better vessel visualization (lack of pruning), observed vasospasm, and reduced vasogenic edema in these patients could suggest that hypertension is acting in a positive fashion to improve cerebral blood flow at some point in the toxicity process. Therefore, the role of hypertension and its contribution to the development of PRES is unclear.

Major Conditions Associated with PRES and Summation of Causes in Transplantation

Most the patients in our overall study population (100 of 106 patients [94%]) developed neurotoxicity and PRES in the setting of a complex systemic condition/illness, including infection, sepsis, shock: 25, chemotherapy: 4, autoimmune disease: 11, CsA/FK-506 (allo-BMT, solid organ transplant, marrow disorders): 49, and eclampsia: 11. The pathophysiologic mechanisms underlying these conditions are similar and include: immune system dysfunction, endothelial activation/injury, and/or a complex cytokine response.^{57,59-66} In eclampsia, immune challenge by the fetus and placenta is well recognized and complex immune reaction to fetal antigen is noted, including T cell, endothelial, and coagulation system activation.⁵⁹⁻⁶¹ A similar response is noted after transplantation, in particular after allo-BMT with a T cell and cytokine response that has been likened to the response to viral or bacterial infection.⁵⁷ In autoimmune diseases, a complex T cell immune and antibody response is felt responsible for most observed abnormality.⁶²⁻⁶⁶

After transplantation, patients are intrinsically exposed to most of the major risk factors we identify associated with PRES. Opportunistic infection is well recognized after transplantation, in particular immediately after transplant.⁶⁷⁻⁶⁹ The effects of cyclosporine/FK-506 and complications of transplantation often coexist, including endothelial injury with systemic effects.⁷⁰⁻⁷² In allo-BMT, a direct effect of chemotherapy may also be present related to local endothelial turnover.^{21,22} A tissue injury response is also noted within the first 7–10 days after preconditioning regimens accompanied by a brief but recognizable cytokine response (IL-2, TNF α , IL-1).⁷³⁻⁷⁷

A markedly altered immune state is present after transplantation including GVHD and graft rejection. Acute GVHD after allo-BMT is generally related to either a T cell-mediated response of the graft to the host (in particular to host endothelium) or a response to the preconditioning regimens.^{17,18,31,32} Cytokines may play a prominent role in this effect (IL-2, IL-6, TNF α , IL-1).^{22,57,73-76} Graft rejection in solid organ transplant is related to the development of both T cell activation and anti-vascular/anti-endothelial antibodies.^{77,78}

Transplants therefore may be experiencing a summation of the fundamental factors that are associated with the development of neurotoxicity and PRES, including infection (opportunistic), immune-related effects, chemotherapy-related effects, and the effects of cyclosporine or FK-506.

Conclusion

PRES occurred after severe infection, sepsis, or shock in 25 (23.6%) of 106 patients with other “associations,” including autoimmune disease, postchemotherapy, cyclosporine/FK-506, and eclampsia. In most patients with available cultures (84%), gram-positive organisms, particularly gram-positive cocci, were identified in organ/tissue culture, blood culture, or both. Normotensive and severely hypertensive patients were present in the I/S/S group. The extent of brain edema graded on CT/MR imaging studies was greater in the normal MAP group and less in patients who were severely hypertensive. Vasospasm was noted at MRA in patients who were severely hypertensive. A combination of spasm and vessel “pruning” was seen in MRA in the normal MAP group, perhaps related to reduced branch visualization secondary to diminished cerebral blood flow.

References

- Bartynski WS, Grabb BC, Zeigler Z, et al. Watershed imaging features and clinical vascular injury in cyclosporin A neurotoxicity. *J Comput Assist Tomogr* 1997;21:872–80
- Bartynski WS, Zeigler Z, Spearman MP, et al. Etiology of cortical and white matter lesions in cyclosporin-A and FK-506 neurotoxicity. *AJNR Am J Neuroradiol* 2001;22:1901–14
- Schwartz RB, Bravo SM, Klufas RA, et al. Cyclosporine neurotoxicity and its relationship to hypertensive encephalopathy: CT and MR findings in 16 cases. *AJR Am J Roentgenol* 1995;165:627–31
- Sanders TG, Clayman DA, Sanchez-Ramos L, et al. Brain in eclampsia: MR imaging with clinical correlation. *Radiology* 1991;180:475–78
- Lin JT, Wang WJ, Fuh JL, et al. Prolonged reversible vasospasm in cyclosporin A-induced encephalopathy. *AJNR Am J Neuroradiol* 2003;24:102–04
- Ito T, Sakai T, Inagawa S, et al. MR angiography of cerebral vasospasm in preeclampsia. *AJNR Am J Neuroradiol* 1994;16:1344–47
- Shengar AR, Gupta RK, Dhanuka AK, et al. MR imaging, MR angiography and MR Spectroscopy of the brain in eclampsia. *AJNR Am J Neuroradiol* 1997;18:1485–90
- Schwartz RB, Jones KM, Kalina P, et al. Hypertensive encephalopathy: findings

- on CT, MR imaging and SPECT imaging in 14 cases. *AJR Am J Roentgenol* 1992;159:379–83
- Rippe DJ, Edwards MK, Schrodt JF, et al. Reversible cerebral lesions associated with tiazofurin usage: MR demonstration. *J Comput Assist Tomogr* 1988;12:1078–81
- Vaughn DJ, Jarvik JG, Hackney D, et al. High-dose cytarabine neurotoxicity: MR findings during acute phase. *AJNR Am J Neuroradiol* 1993;14:1014–16
- Ito Y, Arahata Y, Goto Y, et al. Cisplatin neurotoxicity presenting as reversible posterior leukoencephalopathy syndrome. *AJNR Am J Neuroradiol* 1998;19:415–17
- Hinchey J, Chaves C, Appignani B, et al. A reversible posterior leukoencephalopathy syndrome. *N Engl J Med* 1996;334:494–500
- Provenzale JM, Petrella JR, Cruz LC, et al. Quantitative assessment of diffusion abnormalities in posterior reversible encephalopathy syndrome. *AJNR Am J Neuroradiol* 2001;22:1455–61
- Mukherjee P, McKinstry RC. Reversible posterior leukoencephalopathy syndrome: evaluation with diffusion-tensor MR imaging. *Radiology* 2001;219:756–65
- Covarrubias DJ, Leutner PH, Campeau NG. Posterior reversible encephalopathy syndrome: prognostic utility of quantitative diffusion-weighted MR images. *AJNR Am J Neuroradiol* 2002;23:1038–48
- Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. *Intensive Care Med* 1996;22:707–10
- Munford RS. Sepsis, severe sepsis, and septic shock. In: Mandell GL, Bennett JE, Dolin R eds. *Principles and Practice of Infectious Disease*. Philadelphia: Elsevier; 2005:906–26
- Schwartz RB, Feske SK, Polack JF, et al. Preeclampsia-eclampsia: clinical and neuroradiographic correlates and insights into the pathogenesis of hypertensive encephalopathy. *Radiology* 2000;217:371–76
- Sibai BM. Eclampsia: maternal-perinatal outcome in 254 consecutive cases. *Am J Obstet Gynecol* 1990;163:1049–55
- Gijtenbeek JMM, van den Bent MJ, Vecht CJ. Cyclosporine neurotoxicity: a review. *J Neurol* 1999;246:339–46
- Bartynski WS, Zeigler ZR, Shaddock RK, et al. Pretransplantation conditioning influence on the incidence of cyclosporine and FK-506 neurotoxicity in allogeneic bone marrow transplantation. *AJNR Am J Neuroradiol* 2004;25:261–69
- Bartynski WS, Zeigler RZ, Shaddock RK, et al. Variable incidence of cyclosporine and FK-506 neurotoxicity in hematopoietic malignancies and marrow conditions after allogeneic bone marrow transplantation. *Neurocritical Care* 2005;3:33–45
- Scherrer U, Vissing SF, Morgan BJ, et al. Cyclosporine-induced sympathetic activation and hypertension after heart transplantation. *N Engl J Med* 1990;323:693–99
- Mark AL. Cyclosporine, sympathetic activity, and hypertension. *N Engl J Med* 1990;323:748–50
- Brun-Buisson C, Doyon F, Carlet J, et al. Incidence, risk factors, and outcome of severe sepsis and septic shock in adults. *JAMA* 1995;274:968–74
- Sands KE, Bates DW, Lanke PN, et al. Epidemiology of sepsis syndrome in 8 academic medical centers. *JAMA* 1997;278:234–40
- Rangel-Frausto MS, Pittet D, Costigan M, et al. The natural history of the systemic inflammatory response syndrome (SIRS). A prospective study. *JAMA* 1995;273:117–23
- Cohen J. The immunopathogenesis of sepsis. *Nature* 2002;420:885–91
- Mutunga M, Fulton B, Bullock R, et al. Circulating endothelial cells in patients with septic shock. *Am J Respir Crit Care Med* 2001;163:195–200
- Aird WC. The role of the endothelium in severe sepsis and multiple organ dysfunction syndrome. *Blood* 2003;101:3765–77
- Parent C, Eichacker PQ. Neutrophil and endothelial cell interactions in sepsis. The role of adhesion molecules. *Infect Dis Clin North Am* 1999;13:427–47
- Bannerman DD, Goldblum SE. Mechanisms of bacterial lipopolysaccharide-induced endothelial apoptosis. *Am J Physiol Lung Cell Mol Physiol* 2003;284:L899–914
- Symeonides S, Balk RA. Nitric oxide in the pathogenesis of sepsis. *Infect Dis Clin North Am* 1999;13:449–63
- McCuskey RS, Urbaschek R, Urbaschek B. The microcirculation during endotoxemia. *Cardiovasc Res* 1996;752–63
- Wanecek M, Weitzberg E, Rudehill A, et al. The endothelin system in septic and endotoxin shock. *Eur J Pharmacol* 2000;407:1–15
- Weitzberg E, Lundberg JM, Rudehill A. Elevated plasma levels of endothelin in patients with sepsis syndrome. *Circ Shock* 1991;33:222–27
- Pittet JF, Morel DR, Hensen A, et al. Elevated plasma endothelin-1 concentrations are associated with the severity of illness in patients with sepsis. *Ann Surg* 1991;213:261–64
- Marsden PA, Brenner BM. Transcriptional regulation of the endothelin-1 gene by TNF- α . *Am J Physiol* 1992;262:854–61
- Mantovani A, Bussolino F, Dejanna E. Cytokine regulation of endothelial cell function. *FASEB J* 1992;6:2591–99
- Maemura K, Kurihara H, Morita T, et al. Production of endothelin-1 in vascu-

- lar endothelial cells is regulated by factors associated with vascular injury. *Gerontology* 1992;38(Suppl 1):29–35
41. Sugiura M, Inagami T, Kon V. **Endotoxin stimulates endothelin-release in vivo and in vitro as determined by radioimmunoassay.** *Biochem Biophys Res Commun* 1989;161:1220–27
 42. Battistini B, Forget MA, Laight D. **Potential roles for endothelins in inflammatory response syndrome with a particular relationship to cytokines.** *Shock* 1996;5:167–83
 43. Varon J, Marik PE. **Multiple organ dysfunction syndrome.** In: Irwin RS and Rippe JM, eds. *Intensive Care Medicine.* Philadelphia: Lippincott Williams & Wilkins; 2003:1834–38
 44. Rivers EP, Otero RM, Nguyen HB. **Approach to the patient in shock.** In: Tintinalli JE, Kelen GD, Stapczynski JS, eds. *Emergency Medicine: A Comprehensive Study Guide.* New York: McGraw Hill; 2004:219–25
 45. McGuire TR, Bociek GR, Pavletic SZ, et al. **Organ dysfunction following stem cell transplantation: relationship to plasma cytokine concentrations.** *Bone Marrow Transplant* 2001;28:889–93
 46. Gordon B, Lyden E, Lynch J, et al. **Central nervous system dysfunction as the first manifestation of multiple organ dysfunction syndrome in stem cell transplant patients.** *Bone Marrow Transplant* 2000;25:79–83
 47. Haire W. **The multiple organ dysfunction syndrome in cancer patients undergoing hematopoietic stem cell transplantation.** *Semin Thromb Hemost* 1999;25:223–37
 48. Gabay C, Kushner I. **Acute-phase proteins and other systemic responses to inflammation.** *N Engl J Med* 1999;6:448–54
 49. Eykyn SJ, Gransden WR, Phillips I. **The causative organisms of septicemia and their epidemiology.** *J Antimicrob Chemother* 1990;25:41–58
 50. Wisplinghoff H, Seifert H, Wenzel RP, et al. **Current trends in the epidemiology of nosocomial bloodstream infections in patients with hematological malignancies and solid neoplasms in hospitals in the United States.** *Clin Infect Dis* 2003;36:1103–10
 51. Spanu T, Sanguinetti M, D'Inzeo T, et al. **Identification of methicillin-resistant isolates of staphylococcus aureus and coagulase-negative staphylococci responsible for bloodstream infections with the Phoenix system.** *Diagn Microbiol Infect Dis* 2004;48:221–27
 52. Koth M. **Bacterial pyrogenic exotoxins as superantigens.** *Clin Microbiol Rev* 1995;4:11–426
 53. Sriskandan S, Cohen J. **Gram-positive sepsis. Mechanisms and differences from gram-negative sepsis.** *Infect Dis Clin North Am* 1999;13:397–412
 54. Unnikrishnan M, Altmann DM, Proft T, et al. **The bacterial superantigen streptococcal mitogenic exotoxin Z is the major immunoreactive agent of streptococcus pyogenes.** *J Immunol* 2002;169:2561–69
 55. Bannan J, Visvanathan K, Zabriskie. **Structure and function of streptococcal and staphylococcal superantigens in septic shock.** *Infect Dis Clin North Am* 1999;13:387–463
 56. Cohen SS. **Gram-positive sepsis. Mechanisms and differences from gram-negative sepsis.** *Infect Dis Clin North Am* 1999;13:397–412
 57. Ferrara JLM. **Pathogenesis of acute graft-versus-host disease: cytokines and cellular effectors.** *J Hematother Stem Cell Res* 2000;9:299–306
 58. Martin GS, Mannino DM, Eaton S, et al. **The epidemiology of sepsis in the United States from 1979–2000.** *N Engl J Med* 2003;348:1546–54
 59. Hypertensive disorders in pregnancy. In: Cunningham FG, Gant NF, Leveno KJ, et al, eds. *Williams Obstetrics*, 21st ed. New York: McGraw-Hill; 2001:567–618
 60. Dekker GA, Sibai BM. **Etiology and pathogenesis of pre-eclampsia: current concepts.** *Am J Obstet Gynecol* 1998;179:1359–75
 61. The placenta and fetal membranes. In: Cunningham FG, Gant NF, Leveno KJ, et al, eds. *Williams Obstetrics*, 21st ed. New York: McGraw-Hill; 2001:85–108
 62. Bradley JR, Lockwood CM, Thiru S. **Endothelial cell activation in patients with systemic vasculitis.** *Q J Med* 1994;87:741–45
 63. Pall AA, Savage COS. **Mechanisms of endothelial cell injury in vasculitis.** *Springer-Verlag Semin Immunopathol* 1994;16:23–27
 64. Smith EA. **Systemic sclerosis: etiology and pathogenesis.** In: Hochberg MC, Silman AJ, Smolen JS, et al, eds. *Rheumatology*, 3rd ed. Edinburgh: Mosby; 2003:1481–92
 65. Stone JH, Hoffman GS. **Cellular immunity. Systemic lupus erythematosus.** In: Hochberg MC, Silman AJ, Smolen JS, et al, eds. *Rheumatology*, 3rd ed. Edinburgh: Mosby; 2003:1347–58
 66. Stone JH, Hoffman GS. **Wegener's granulomatosis and lymphoid granulomatosis.** In: Hochberg MC, Silman AJ, Smolen JS, et al, eds. *Rheumatology*, 3rd ed. Edinburgh: Mosby; 2003:1624–34
 67. Burt RK, Walsh T. **Infection prophylaxis in bone marrow transplant recipients—myths, legends, and microbes.** In: *On Call in Bone Marrow Transplantation.* Burt RK, Deeg HJ, Lothian ST, et al, eds. Georgetown, Tex: Landes Bioscience; 1996:439–451
 68. Burns WH. **Virus infections complicating bone marrow transplantation.** In: *On Call in Bone Marrow Transplantation.* Burt RK, Deeg HJ, Lothian ST, et al, eds. Georgetown, Tex: Landes Bioscience; 1996:439–451
 69. Stosor V. **Infection in transplant recipients.** In: *On Call in Bone Marrow Transplantation.* Burt RK, Deeg HJ, Lothian ST, et al, eds. Georgetown, Tex: Landes Bioscience; 1996:399–425
 70. Ramanathan V, Helderma JH. **Cyclosporine formulations.** In: Sayegh M, Remuzzi G, eds. *Current and Future Immunosuppressive Therapies following Transplantation.* Netherlands: Kluwer Academic; 2001:111–21
 71. Shapiro R. **Tacrolimus.** In: Sayegh M, Remuzzi G, eds. *Current and Future Immunosuppressive Therapies following Transplantation.* Netherlands: Kluwer Academic; 2001:123–42
 72. Holler E, Kolb HJ, Hiller E, et al. **Microangiopathy in patients on cyclosporine prophylaxis who developed acute graft-versus-host disease after HLA-identical bone marrow transplantation.** *Blood* 1989;73:2018–24
 73. Hill GR, Crawford JM, Cooke KR, et al. **Total body irradiation and acute graft-versus-host disease: the role of gastrointestinal damage and inflammatory cytokines.** *Blood* 1997;90:3204–13
 74. Antin JH, Ferrara JLM. **Cytokine dysregulation and acute graft-versus-host disease.** *Blood* 1992;80:2964–68
 75. Holler E, Kolb HJ, Moller A, et al. **Increased serum levels of tumor necrosis factor α precede major complications of bone marrow transplantation.** *Blood* 1990;75:1011–16
 76. Schots R, Kaufman L, Van Riet I, et al. **Proinflammatory cytokines and their role in the development of major transplant-related complications in the early phase after allogeneic bone marrow transplantation.** *Leukemia* 2003;12:1150–56
 77. Halloran PF, Batiuk TD, Goes N, et al. **Immunologic concepts.** In: Stuart FP, Abecassis MM, Kaufman DB eds. *Organ Transplantation.* Georgetown, Tex: Landes Bioscience; 2003:1–44
 78. Cerilli J, Brasile L, Galouzis T, et al. **The vascular endothelial cell antigen system.** *Transplantation* 1985;39:286–89