CLINICAL STUDY

Renal rescue therapy in early stage of severe sepsis: a case study approach

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Abstract

Objective: **The aim of this study was to evaluate the efficacy of noradrenaline and furosemide in combination for the treatment of impending acute renal failure in early stage of severe sepsis.**
Design: **observational case study.**
Setting: **Nine-bed general ICU in university-affiliated cancer institute. Patients: Severe septic cancer patients admitted to the ICU.**
Measurments and results: **17 severe septic patients with multiorgan dysfunction syndrome (admission SOFA score, mean 9.1±3.0 p, and APACHE II score, mean 20.4±5.1 p.) received full intensive treatment including volume expansion, hemodynamic support with noradrenaline infusion and low-dose hydrocortisone. Severe sepsis was documented by proven infection, site of infection and high levels of procalcitonin (mean value 69.8 ng/ml, 7.1–588 ng/ml), C-reactive protein (mean 210 mg/l, range 49–370 mg/l) and low total cholesterol levels (mean 2.36 mmol/l, range 1.3–3.9 mmol/l). Acute renal injury and acute renal failure syndrome were detected in 14 patients (82 %) out of 17. The combination of noradrenaline continuous infusion (0.06–0.12 μg/kg/min) and furosemide infusion (10–30 mg/hr) was used for hemodynamic and renal support. We induced polyuria and reverse acute tubular necrosis to nonoliguric acute renal failure in 11 patients (78.5 %) from 14 septic cancer patients with acute renal injury/failure syndrome. We recorded 35.2 % hospital mortality due to the severe sepsis and septic shock. We used no renal replacement therapy.**
Conclusion: **We consider renal rescue protocol as an effective method in the treatment for acute renal injury/failure syndrome in early phase of severe sepsis, when it is instituted very early with low/moderate dosage of noradrenaline and furosemide.** ***(Tab. 6, Ref. 29.)***
Key words: severe sepsis, SOFA score, acute renal failure, noradrenaline, Furosemide, renal rescue protocol.

Severe sepsis is characterized by wide clinical heterogeneity in severity of illness, underlying infectious etiology, inadequate systemic inflammatory immune response (hyper- and/or hyporesponsivness) and multiple organ dysfunction syndrome. Sepsis is a common cause of acute renal failure (Cunnigham et al, 2000; Murray, 2003). Acute renal failure in early phase of severe sepsis occurred in 42–55 % septic patients and is associated with significant influence on sepsis mortality (Dhainaut et al, 2003; Padkin et al, 2003). Acute renal failure (ARF) markedly increased mortality of septic patients with multiorgan dysfunction syndrome: mortality reached 60 % in two dysfunctional organ systems, and 70 to 79 % in three failing organs when one organ is kidney (Padkin et al, 2003). Hospital mortality in severe septic patients with ARF, approximately 75 %, is significantly higher than mortality (45 %) in septic patients without ARF ($p<0.001$). Improving renal function during severe sepsis may substantially improve overall mortality in severe sepsis (Dhainaut et al, 2003; Padkin et al, 2003).

Appropriate therapy of severe sepsis may rescue the kidney function and markedly improve patient outcome. Many studies

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Tab. 1. Acute renal dysfunction criteria for acute renal injury and acute renal failure according to Bellomo et al (2001). UO – urine output, RRT – renal replacement therapy, ARI – acute renal injury, ARF – acute renal failure.

Acute Renal Failure Syndrome (ARFs)			
Normal	Acute renal injury	Acute renal failure moderate	Acute renal failure severe
Normal creatinine (<120 μmol/l) Normal urea (<8 mmol/l) Normal urine output >800 ml/day	Elevated creatinine (>120 μmol/l) and urea (>8 mmol/l) UO<800 ml/24 hrs UO<200 ml/6 hrs	Elevated creatinine (>240 μmol/l) and urea (>16 mmol/l) UO<400 ml/24 hrs UO<100 ml/ 6 hrs	Need for RRT and either ARI or ARF syndrome criteria

have demonstrated the beneficial effects of noradrenaline on renal function during septic shock (Desjars et al, 1987; Meadows et al, 1988). Many intensivists clearly showed effectivness of noradrenaline to treat septic shock and save kidney function (Cesare et al, 1993; Redl-Wenzl et al, 1993; Martin et al, 1990, 2000). While hemodynamic support with noradrenaline is widely accepted, the early renal support with loop diuretics is debatable. The meta-analysis of clinical data does not support the overall use of loop diuretics (Mehta et al, 2002; Kellum, 2002). Our clinical experiences are in opposite to this claim.

We adopted renal rescue managment of impending acute renal failure as a part of therapy in early phase of severe sepsis or septic shock, which is based on volume expansion and continuous infusion of noradrenaline and furosemide to reverse initial ARF (Cordingley and Palazzo, 1998). This approach was clinically verified in cardiac surgery patients with acute renal failure during postoperative period (Halaj et al, 2000). We demonstrate our approach how to maintain renal function during severe sepsis and septic shock by a complex of hemodynamic, renal and metabolic/nutritional support.

Patients and methods

We analyzed the records of 17 consecutive critically ill cancer patients with severe sepsis and septic shock (diagnostic criteria according to ACCP/SCCM consensus conference 1991) admitted to our 9 bed surgical-medical ICU in the university-affiliated hospital.

Following information were collected at baseline from the cancer septic patients: age, gender, underlying disease, blood lactate, blood urea and creatinine, urine flow, heart rate, mean arterial pressure and central venous pressure, blood gas analysis and acid base balance. Surrogate biomarkers of sepsis including procalcitonin and C-reactive protein, have been followed during 24–48 hours of severe sepsis (Zahorec et al, 2001). Other variables were collected 24–48 hours after the ICU admission: Acute Physiology and Chronic Health Evaluation (APACHE) II score and Sepsis related Organ Failure Assessment (SOFA) score (Janssens et al, 2000). We followed ICU mortality, hospital mortality and 60-day mortality. We monitored in all patients heart rate (ECG), invasive arterial blood pressure, central venous pressure, body temperature, pulse oximetry, urine flow per hour and per day. Urine was collected via an indwelling bladder catheter. Urine biochemical parameters were measured every 24 hours including creatinine and urea in urine, mineral urine excretion. We calculated creatinine clearence, water and sodium excretion fraction (not shown).

Acute renal failure is a gradual process with developing pathogenesis. ARF is a syndrome and the degree of kidney injury is dependent on inducing etiopathogenic factors including the time component of renal injury e.g. duration of shock and ischemia (Bellomo et al, 2001). Renal dysfunction should be evaluated according to duration and severity of injury. Bellomo et al (2001) suggested a simple approach to the evaluation of the acute renal dysfunction in critically ill patients. The surrogate parameters of renal dysfunction involve only urea, creatinine, and urine output. We diagnosed acute renal injury (ARI) and acute renal failure (ARF) syndrome according to proposed criteria for acute renal injury (mild dysfunction) and acute renal failure (moderate and severe renal failure) syndrome (Tab. 1).

We treated 17 severe septic patients: 11 surgical and 6 medical patients. All patients received antimicrobial therapy: we started with initial broad-spectrum antibiotics and when cultures results were obtained the antibiotic/antimycotic regimen was adjusted. Mechanical ventilation was performed on Evita 2 Drager, hemodynamic monitoring on Siemens 9000XL monitors.

Hemodynamic managment was directed according to arterial and venous pressures and heart rate, based on the priciples of functional hemodynamic monitoring and managment (Pinsky, 2002). Initially, the septic patients were given fluid resuscitation with crystalloids (lactated Ringers solution) and colloids (6 % hydroxyethylstarch and 1–2 units of fresh frozen plasma). Within the first hour after volume expansion and sustained hypotension (MAP<65 mmHg) continuous infusion of noradrenaline was started (low or medium dose 0.06–0.12 μg/kg/min). In case of continuous oliguria (less than 30 ml/hr in two consecutive hours) and after increased systemic arterial blood pressure (MAP>80–85 mmHg) continuous furosemide infusion started in dose 30–40 mg/hr. All patients received low dose corticoid therapy (Hydrocortisone 3x50–100 mg/day adjusted to body weight). Hemodynamic and renal support managment is summarized on Table 2. The goals of oxygen and hemodynamic variables include: pulse

Tab. 2. "Bratislava protocol" for the renal rescue therapy of impending acute renal failure due to severe sepsis and septic shock. FFP – fresh frozen plasma, RBCs – red blood cells.

Renal Rescue Therapy for Acute Renal Failure in Severe Sepsis and Septic Shock		
Goal of the treatment	Drugs and fluids	Dosage of fluids and drugs
Correction of hypovolemia (according to CVP, pulse pressure), volume expansion	Colloids and crystaloids (volume ratio 1:2 or 1:3)	Artificial colloid 4–5 ml/kg FFP 1–2 units, 3–6 ml/kg Fresh RBCs 1–2 units/day
Hemodynamic support (maintain MAP>85 mmHg)	Noradrenaline continuous infusion in combination with dobutamine and/or vasopressin(terlipressin)	0.05-0.15 µg/kg/min (Noradr) 5–10 µg/kg/min (Dobutamin)
Renal support (maintain diuresis 2–3 ml/kg/hr)	Furosemide contin. infusion in combination with bolus	10–50 (–80) mg/hr 125–250 mg/6 hrs
Correction of homeostasis disturbances (metabolic acidosis, hyponatremia,hypoproteinemia)	4.2% bicarbonate infusion calcium gluconicum inf. fresh frozen plasma (FFP)	2–3 ml/kg 10–20 ml/day 4–6 ml/kg
Metabolic support Nutrition support	10% or 20% glucose 10% or 20% lipid emulsion Insulin contin. infusion	100–200 g/day 250–500 ml/day 4–9 units/hr
Endocrinne support	Hydrocortison bolus inj. Aldacton bolus inj. Metoclopramid inj	3x1–2 mg/kg/day 1–2 x 200 mg/day 2x10 mg/day

oxygenation >93 %, venous oxygen saturation >70 %, MAP>80–85 mmHg, heart rate <110 beats/min and urine output >1.5–2 ml/kg/hr. The main goal is to induce or maintain diuresis higher than 100 ml/hr in adult septic patients. When hemodynamic status of patients was stable for 16–24 hours, progressive withdrawal of the drugs (noradrenaline, furosemide) was started. After withdrawal of vasopressores, we continued with cardiotonic-diuretic therapy using digoxine and cancreolate (Aldacton iv).

Results

From the 17 patients were 5 men and 12 women with a mean age of 61.5±10 yrs. The mean SOFA score was 9.1±3.1 and 8.76±3.6 p. on the day of ICU admission and 1st ICU day. The mean APACHE II scores were 20.4±5.1 and 17.2±4.9 points for the first two ICU days. The causes of severe sepsis/septic shock were in 9 cases peritonitis (52.9 %), in 3 pneumonia and febrile neutropenia (17.6 %), 2 cases of bacterial endocarditis (11.8 %) and in 2 kidney and urinary tract infection (11.8 %). 9 patients needed prolonged (>6 hours) mechanical ventilation. Demographic data are presented in Table 3. Diagnosis of severe sepsis and septic shock was supported by at least 3 SIRS criteria, documented infection, source of infection and presence of organ dysfunction or failure. We routinely followed inflammatory markers, which demonstrate severe inflammatory – immune response during severe sepsis and septic shock (Tab. 4). Severe sepsis is documented by very high serum concentration of procalcitonin (7.1–588 ng/ml, mean value 69.8 ng/ml on the day of ICU admission) and high serum levels of C-reactive protein (49–370 mg/l, mean value 210 mg/l). A remarkable biochemical finding was low total cholesterol serum level in severe septic oncologic patients. We recorded significant hypocholesterolemia (1.3–3.9 mmol/l, mean 2.36 mmol/l). 8 patients had absolute or relative leukopenia (inadequate increase of blood leukocyte counts to the systemic infection). 4 septic patients suffered from febrile neutropenia (pts 4, 6, 9, 16), and severe sepsis was a complication of chemotherapy induced severe neutropenia or pancytopenia (pts 4, 6, 16). Severe sepsis is associated with marked decrease of albumine levels. Hypoalbuminemia has reached nadir values during the first 24 hours of severe sepsis/septic shock (16.5–32 g/l, mean 23.0 g/l). The time course of selected laboratory parameters during first 24 hours of severe sepsis is presented in Table 4.

Mortality on ICU was 29.4 % (5 pts/17pts), overall hospital mortality has reached 35.3 % (6/17 pts) and 60-days mortality rate was 41.2 % (7/17 pts). 2 deaths could not be avert due to advanced abdominal cancer and unsuccessful surgery (pts 1, 9). Both patients with bacterial endocarditis died of cardiac causes: one death from mitral valve obstruction with big endocardial thrombus after clinical improvement from severe sepsis (pt 7),

Tab. 3. Demographic and clinical data of 17 severe septic patients. SOFA and APACHE score expressed in points during the first 2–3 ICU days. Gender: F – female, M – male sex, Dg – primary diagnosis according to International Code of Diseases (K65 – peritonitis, J15 – bronchopneumonia, I39 – bacterial endocarditis, N17 – pyelonephritis, infection of urinary tract). Values expressed as a median and 25–75 % percentil range, or as a mean±standard deviation.

Demographic data of cancer patients with severe sepsis and septic shock

Pt	Sex	Age years	Dg	Sev.sepsis sept.shock	SOFA points	APACHE II points	ICUstay days	ICU outcome
1	F	77	K 65	sept.shock	14,15	23,24	2	died
2	F	50	K 65	sev.sepsis	6,5,3	13,10,9	4	survived
3	F	49	K 65	sev.sepsis	7,5,5	23,16,9	13	survived
4	M	68	J 15	sept.shock	12,13,13	23,15,11	7	survived
5	F	49	K 65	sept.shock	7,5,4	20,10,7	8	survived
6	M	52	J 15	sev.sepsis	8,9,17	17,23,26	3	died
7	M	68	I 39	sev.sepsis	10,7	19,13	2	died
8	F	71	N 17	sept.shock	10,12,11	18,17,11	11	survived
9	F	67	K 65	sept.shock	15,14	25,26	2	died
10	F	38	J 15	sev.sepsis	5,5,5	16,15,12	20	survived
11	F	62	K 65	sev.sepsis	7,7,5	19,16,14	15	survived
12	M	62	N 17	sept.shock	8,8,10	18,15,15	8	survived
13	F	68	I 39	sept.shock	12,13,17	35,26,26	14	died
14	F	73	K 65	sev.sepsis	6,6,8	23,18,15	7	survived
15	F	63	K 65	sev.sepsis	6,6,6	13,14,12	8	survived
16	F	66	J 15	sept.shock	12,12,9	22,17,16	7	survived
17	M	62	K 65	sev.sepsis	10,7,6	21,17,14	17	survived
75 %		68 yrs			12,12p	23,18p	13days	
median		63 yrs			8,7p	20,16p	8days	
25 %		52 yrs			7,6p	18,15p	4days	
Mean±SD		61.5±10 yrs			9.1,8.76p	20.5,17.2p	8.7±5.5days	

Tab. 4. Selected laboratory parameters (two values for each pt) during the first 24 ICU hours: 1st value – at ICU admission, 2nd value following 12–24 hours later. WBC – white blood cells count- x10^9 /L, Plt-platelet counts - x10^9/L, serum creatinine – µmol/L, albumin – g/L, PCT – procalcitonin ng/ml, C-reactive protein – mg/l, lactate – mmol/l, Chol – cholesterol mmol/L. Laboratoty tests for severe sepsis monitoring according to Zahorec et al (2001).

Laboratory data in early phase of severe sepsis.

Pt	WBC	Plt ser.	Creat.	Albumin	PCT	CRP	Lactate	Chol
1	6.3/2.1	249/173	154/211	19.0/20.0	63.1/91	185/219	10.6/-	1.9/1.8
2	3.3/10.8	88/101	105/96	25.4/24.0	9.2/15.5	159/143	-/-	3.4/3.9
3	5.4/8.1	145/87	118/108	24.8/26.1	113/102	69/68	3.9/3.3	1.76/1.6
4	0.2/0.27	6/6	341/382	21.0/28.2	74/60.5	-/-	6.4/2.9	2.4/2.9
5	2.6/4.4	90/153	95/105	23.0/27.0	29/40.1	96/-	7.2/1.8	1.4/1.4
6	0.3/0.2	47/32	184/295	20.0/21.0	2.4/7.5	273/355	1.2/1.6	3.8/3.6
7	24.1/13.1	193/148	122/124	30.0/26.0	4.5/11.2	139/-	1.9/8.6	3.3/3.2
8	27.1/21.1	116/99	563/512	32.0/33.0	588/357	198/163	3.6/3.1	3.9/3.8
9	2.0/1.2	177/141	178/212	28.0/30.0	14.3/22.1	49/55.6	12.5/15	2.9/2.7
10	12.1/14.4	110/95	102/98	24.0/16.4	4.5/7.6	370/264	-/-	1.7/1.7
11	24.1/17.1	529/422	143/137	19.0/20.0	7.1/5.2	292/215	2.0/1.4	1.2/1.5
12	25.8/29.1	245/164	179/274	21.0/18.2	158.1/118	293/310	2.3/1.7	2.3/2.3
13	23.2/19.9	207/91	278/263	21.8/22.6	12.4/210	-/177	11.7/3.8	2.0/1.6
14	20.9/21.2	138/118	83/98	22.0/22.0	7.1/8.8	-/-	4.6/1.5	2.2/1.3
15	6.3/12.3	169/165	154/168	24.0/24.1	8.7/5.6	301/294	2.7/-	1.7/2.8
16	23.2/19.9	10/12	178/177	21.2/18.3	88.5/52.8	303/308	4.7/3.1	2.9/2.9
17	9.9/21.1	195/244	97/121	16.5/17.7	2.6/7.1	212/189	1.9/1.7	1.3/1.7

Tab. 5. Some renal function parameters during first 24–48 hours in severe septic patients. ARI – acute renal injury, ARF – acute renal failure, N – normal kidney function, according to Bellomo et al (2001).

Diuresis and renal functions in early phase of severe sepsis (first 24–48 hrs)											
Pt ICU day	Average diures. 0	hour ml/h 1	Diuresis ml/day 0	1	Creatinine clear. ml/s 0	1	Urine creat. mmol/l 0	1	Urea serum mmol/l 0	1	ARI/ARF syndrome
1	5-10	0	260	15	0.01	-	0.36	-	12.5	16.8	ARF
2	130	130	3300	3450	0.81	0.78	2.17	1.76	8.4	12.2	ARI
3	60	50	1440	1260	0.71	0.57	-	-	5.9	8.8	ARI
4	13	130	330	3180	0.11	0.22	-	-	33.0	26.9	ARF
5	15-80	83	1780	2000	0.9	1.22	4.18	4.26	6.0	7.7	N
6	90-50	10	1350	130	1.3	0.36	3.17	2.73	5.4	13.9	ARF
7	140	166	3520	3990	1.21	1.18	4.57	4.51	5.4	8.4	N
8	10	15-20	150	460	0.08	0.06	2.35	1.45	34.1	38.5	ARF
9	25	5-10	410	110	0.34	0.31	2.1	1.5	11.0	11.7	ARF
10	100	122	1000	2940	1.45	1.6	4.41	4.45	8.4	7.9	N
11	10-40	175	420	4190	0.59	0.72	1.68	2.3	15.1	13.1	ARI
12	10-20	170	200	4080	0.6	0.71	4.8	1.62	10.9	14.9	ARF
13	60-10	20-35	1090	760	0.21	0.15	2.28	2.04	14.9	16.1	ARF
14	80-13	70-80	2700	1720	0.61	0.78	2.1	1.81	8.4	14.4	ARI
15	30-40	70-85	700	1950	0.57	0.64	3.5	3.3	11.7	14.7	ARI
16	12-30	110-200	1240	3880	0.15	0.18	0.95	1.2	12.2	18.9	ARF
17	20-40	200-280	1070	4380	0.83	0.81	4.11	1.62	9.7	11.7	ARI

the second patient died from prolonged ventricular fibrillation and cerebral death on the 14th day (pt 13). Patient 6 with severe febrile neutropenia died from intractable septic shock. Patient 16 was successfully treated for septic shock. She was discharged from ICU to general ward with full recovery of circulatory, respiratory and renal functions. She died at the oncologic ward 10 days later from the complications of advanced cancer (non-Hodgkin B lymphoma with multiple metastases).

Renal dysfunction in sepsis and SIRS involves various degrees of kidney damage (Bellomo et al, 2001). Bellomo et al (2001) suggested three degrees of kidney dysfunction: mild - acute renal injury, moderate, and severe acute renal failure syndrome. Only 3 patients (17.7 %) out of 17 patients with severe sepsis and septic shock had normal renal functions. 14 patients (82 %) had various degrees of acute renal dysfunction: 6 patients (35.3 %) fulfilled the criteria for acute renal injury – mild renal dysfunction, and 8 patients (47 %) had moderate and severe ARF according to the Bellomo et al criteria. In the treatment for ARI we usually used furosemide boluses (4–6 times/day), the treatment for impending acute renal failure developing due to severe sepsis needs continuous infusion of furosemide after blood pressure restoration with noradrenaline infusion. Our treatment for ARI/ARF due to severe sepsis was successful in 14 patients (82.3 %). In 12 septic patients we induced polyuria (2–4 ml/kg/hr or 3000–4400 ml/day) within 4–8 hours of aggressive therapy with noradrenaline and furosemide. Polyuria in one patient was induced after 12 hours (pt 4). The most resistant to the kidney rescue therapy was patient 8 with previous chronic renal failure and hypertension. The restoration of diuresis was successful after 36 hours of intensive treatment with noradrenaline (0.12 μg/kg/min), furosemide (80 mg/hr and boluses 125 mg) and sodium loading (4.2 % $NaHCO_3$ and 10 % NaCl), when mean arterial pressure exceeded 100 mmHg. In 11 septic patients sensitive renal tests (sodium and water excretion fraction) confirm nonoliguric acute renal failure. We used no renal replacement therapy.

Other three patients died from intractable septic shock (pts 1, 6, 9) with oliguria (17.7 %), when surgery was not successful, we lost the control under the source of infection and/or due to the advanced cancer. These patients died within 24–48 hours from irreversible shock. *Bratislava renal rescue protocol* seems to be effective in managment of ARF due to the severe sepsis in early phase (first 12–24 hours of developing severe sepsis), but it should be verified on larger multicentric clinical studies.

Discussion

The underlying mechanisms of ARF in severe sepsis is acute tubular necrosis (ATN). Pathogenesis of acute tubular necrosis in severe sepsis is mutlifactorial including prerenal (hypovolemia, hypotension, hypoxia and ischemia), endocrine and renal causes: deleterious effects of putative mediators of systemic inflammation like endotoxin, complement activation, TNF, nitric oxide, endotelin-1, thromboxanes and leukotrienes on renal microcirculation and kidney tubular cells (Cunnigham et al, 2000). Hospital mortality of septic patients with MODS and ARF is markedly higher than in septic patients with MODS without ARF (75 % vs 45 %, $p<0.001$) (Padkin et al, 2003). This observation justifies the main goal of our clinical study: the developing ARF should be treated adequately in early phase of severe sepsis and septic shock. We suggest an approach based on the "*Charing Cross"* renal rescue protocol (Cordingley and Pallazo, 1998),

Tab. 6. Hemodynamic and renal support in early stage of severe sepsis and septic shock (the course of first 24 hrs on ICU). NA – noradrenaline, DOP – dopamine, DOB – dobutamine, FUR – furosemide, FFP – fresh frozen plasma, RBC – red blood cells transfusion, Haes – 6 % HAES steril, Alb – albumin, the dose of vasopressors and/or inotropics are expressed in µg/kg/min.

Pt	Type of pts	Fluids (colloids)	Hemodynamic support	Renal support	Hospital outcome
1	surgical	FFP 1U, Alb	NA 0.08, DOP 8.0	FUR bolus 40-80 mg	died
2	surgical	FFP 2U, RBC	NA 0.05, DOP 3.0	FUR bolus 3x20 mg	survived
3	surgical	FFP 2U, Alb	NA 0.2-0.04	FUR bolus 4x10 mg	survived
4	medical	FFP 2U, Plt RBC 2U	NA 0.12-0.05 DOP 2.5-3.0	FUR cont. 25-30 mg/h	survived
5	surgical	FFP 2U, Haes	NA 0.11-0.05	FUR cont. 4x5 mg	survived
6	medical	FFP 1U, Plt	NA 0.1, DOP 6.0	FUR bolus 4x10 mg	died
7	medical	FFP 1U, Haes	DOB 5-6.0	FUR cont. 15-25 mg/h	died
8	medical	FFP 2U, Haes 4.2 % NaHCO	NA 0.1-0.15 DOP 2.0-3.0	FUR cont. 40-80 mg/h + bolus 4x125 mg i.v.	survived
9	medical	FFP 1U, RBC	NA 0.1-0.45	FUR bolus 3x10 mg	died
10	surgical	FFP 1U, RBC	NA 0.1-0.04	FUR bolus 8x10 mg	survived
11	surgical	FFP 3U, Haes	NA 0.11-0.07	FUR cont. 50-20 mg/h	survived
12	medical	FFP 1U	NA 0.11-0.09	FUR cont. 40-30 mg/h	survived
13	medical	FFP 1U	NA 0.06-0.18	FUR cont. 15-30 mg/h	died
14	surgical	FFP 2U, RBC	NA 0.04-0.07	FUR bolus 3x10 mg/d	survived
15	surgical	FFP 1U, Haes	NA 0.05-0.10	FUR bolus 3x20 mg/d	survived
16	medical	FFP 2U, Plt	NA 0.11	FUR cont. 40-10 mg/h	died
17	surgical	FFP 1U, RBC	NA 0.09-0.05	FUR cont. 10-5 mg/h	survived

which enables to maintain and/or restore the kidney function during severe sepsis, including correction of hypovolemia, hypoxemia, as well as to maintain mean arterial blood pressure and perfusion pressure with noradrenaline infusion, and renal support with continuous furosemide infusion. We extended this approach by the correction of oncotic/osmotic (e.g. transfusion of fresh frozen plasma) and ionic disturbances, metabolic/nutrition support of kidney and overall endocrinne support (infusion of insulin with strict control of glycaemia and low-dose hydrocortisone boluses).

The combination of noradrenaline and furosemide appears effective and safe in the treatment of impending ARF due to the systemic inflammatory response syndrome (Cordingley and Palazzo, 1998; Halaj et al, 2000) as well as in the treatment of the hepatorenal syndrome type 1 (Durkin et Winter, 1995; Duvoux et al, 2002). The rationale to use the combination of noradrenaline and furosemide for treatment of impending ARF due to severe sepsis is supported by many experimental and clinical data. The reappraisal of the noradrenaline use in human septic shock was elicited 16 years ago (Desjars et al, 1987; Meadows et al, 1988). Noradrenaline is an effective vassopressor in restoration of central and regional blood pressures. During a septic shock the urine flow is decreased as a result of lowered glomerular filtration pressure. Noradrenaline has a greater effect on efferent than on afferent arteriolar resistance and filtration pressure increase, and it could effectively reestablish the urine flow (Cesare et al, 1993; Martin et al, 1990, 2000). The increase in urine output could be explained by a decrease in antidiuretic hormone release by prompt restoration of adequate sytemic and regional pressures in patients with severe sepsis and septic shock (Martin et al, 1990, 2000). Noradrenaline has better metabolic and immunologic profile than adrenaline or dopamine: noradrenaline induces neither marked hyperlactatemia like adrenaline nor immunodepression like dopamine (Rontgen et al, 2003; Ensinger and Trager, 2002).

Furosemide significantly increased renal medullary pO_2 measured by oxygen microelectrode in rat kidney. Furosemide 3–10 mg/kg selectively enhanced medullary oxygen availability probably by reduction of transport activity and metabolic requirements by medullary ascending limb (Brezis et al, 1994). Furosemide increases central systemic sympathetic nervous activity by releasing adrenaline and noradrenaline (Ueno et al, 1983). Furosemide attenuates the sensitivity to noradrenaline on arteries and antagonizes NA-induced contraction by decreasing calcium content in arteries (Petrusewicz et al, 1985). Intravenous furosemide markedly reduces sympathetic vasoconstrictor responses to both noradrenaline and angiotensin II, which results in inhibition of peripheral sympathetic vasoconstrictor responses (Gerkens, 1984, 1987). The physiologic effects of furosemide on central sympathetic activity, attenuation of vasoconstriction of peripheral arteries, decreasing metabolic requirements of tubular cells and increasing medullary oxygen availability may be a useful tool in the treatment of impending acute renal failure due to sepsis in the early phase.

Observational studies conducted by Martin et al (1990, 2000) clearly demonstrate the effectivness of noradrenaline as a key drug for hemodynamic and renal support in severe sepsis and septic shock. A few papers were published about clinical effectivness to use noradrenaline and furosemide in the treatment of impending acute renal failure due to SIRS and/or in acutely oliguric patients (Cordingley and Palazzo, 1998; Halaj et al, 2000), or due to hepatorenal syndrome type 1 (Durkin and Win-

ter, 1995; Duvoux et al, 2002). However, inappropriate use of noradrenaline and furosemide may have detrimental effects on patients. The use of these drugs in patients with uncorrected dehydratation, or hypovolemia may cause serious damage to vital organs. Too late administration of noradrenaline (more than 24 hours after ICU admission, median 40 hrs) and very high dosage of vasopressors lead to significantly higher mortality of critically ill patients (Abid et al, 2000). Our strategy to treat human septic shock is based on immediate intravascular volume loading, early institution of continuous noradrenalin infusion in low or medium dosage (0.05–0.12 μg/kg/min) and 1–2 hrs later, after blood pressure restoration (MAP higher than 85–90 mmHg) we begun with furosemide continuous infusion (10–30 mg/hr, or more 50–80 mg/hr) to reach adequate urine output (1.5–2 ml /kg/hr). All procedures including invasive monitoring and institution of volume, hemodynamic and renal support should not exceed 2–3 hours. Early diagnosis of septic shock and adequate therapy in early phase (few hours) of severe sepsis may prevent death or attenuate further development of MODS. Our clinical experience confirms real benefit of early hemodynamic and renal support to the severely septic patients, in accordance with recent clinical studies (Rivers et al, 2001). Some authors refuse the early use of loop diuretics as effective therapeutic approach in acute renal failure (Mehta et al, 2002). The late therapy of acute renal failure with loop diuretics was associated with higher mortality of critically ill patients. The analyses of clinical data have revealed that those patients had lower blood pressure, significantly lower cardiac output and cardiac index and a higher occurrence of chronic cardiac failure. Even the propensity score could not eliminate the significant differences in acute and chronic health status between both groups (Mehta et al, 2002). We also conclude that clinical data obtained from this heterogenous group of critically ill patients, where causes of acute renal failure have various origins, are not applicable to the group of severely septic patients. On the other hand this multicentric clinical study is very valuable, because it has clearly shown that the use of diuretics in case of low cardiac output states or low perfusion pressure may be harmful to patients and is markedly associated with higher mortality (Mehta et al, 2002). As mentioned above also inappropriate use of vasopressors (too late administration and high dosage of noradrenaline) is connected with higher mortality (Abid et al, 2000). Renal dysfunction during severe sepsis is a gradual process with three main etiopathogenic causes: pre-renal (hypovolemia, hypotension, ischemia), renal (direct effect of endotoxin and main inflammatory mediators like activated complement, cytokines, big-endotelin) and endocrinne origin (overshoot action of arginine-vasopressin, aldosteron etc.). Kidney is a very sensitive organ to detect circulatory (hemodynamic) and severe systemic inflammatory response. Diuresis and hourly measured urine output is a simple, valuable parameter to detect renal dysfunction together with blood urea and creatinine levels.

We suggested renal rescue protocol to maintain or restore the kidney function during severe sepsis and septic shock, when acute renal failure often developed. We adopted a clinical evidence of beneficial effects of noradrenaline (Redl-Wenzl et al, 1993; Cesare et al, 1993; Martin et al, 1990, 2000; Cordingley and Palazzo, 1998), together with results of furosemide infusion in animal experiments (Brezis et al, 1994) and clinical experiences (Halaj et al, 2000; Duvoux et al, 2002) to create a complex renal rescue protocol.

Kidney rescue therapy for impending acute renal failure in early phase of severe sepsis involves three therapeutic steps (fluid resuscitation, noradrenaline continuous infusion and furosemide bolus or continuous infusion) to reach three goals (adequate volemia, appropriate systemic blood pressure and perfusion pressure, sufficient diuresis) (Cordingley and Palazzo, 1998). Bellomo et al (2001) and Rivers et al (2001) have shown that the time component has a crucial effect on further morbidity and mortality of septic patients. Early managment of severe septic patient should take 2–3 hours, and the critical 3–4 therapeutic steps should be done in few hours (see *Bratislava protocol* in Table 2). Our clinical experience along with other clinical data (Redl-Wenzl et al, 1993; Martin et al, 1990, 2000) provide the evidence that kidney rescue therapy is useful in standard care for severely septic patients. All procedures should be done to prevent further deterioration of organ dysfunction and failure, including kidney. The restoration of kidney function in severe sepsis may substantially improve morbidity and mortality (Padkin et al, 2003). The effectivness of renal rescue protocol to treat impending ARF in early stage of severe sepsis needs further clinical and experimental studies.

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