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ORIGINAL ARTICLE

Nephrology in Bosnia and Herzegovina: impact of the 1992–95 war

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ABSTRACT

It has now been more than two decades since the end of the 1992–95 war in Bosnia and Herzegovina. This may well be the proper time to provide the nephrology community with an appraisal of the care of patients with chronic kidney disease in the pre-war, war and post-war periods in the European transitional country. This report on nephrology in Bosnia and Herzegovina draws attention to the hurdles faced for three turbulent years on that burdensome path of providing quality care, and the chance it offered in developing a successful transplant programme while facing the dreadful chaos of war and a migrant crisis. The perception of war and natural disasters is quite different, from the victim's point of view, from the standardized and well-arranged healthcare systems in the developed world. The guidelines, written in peace, are extremely useful, but are often hard to follow during natural disasters or barbarous wars. Each of the periods described had its specificities as well as its good and bad sides. Despite the unquestionable destructive nature of the war, it was a catalyst for nephrology in Bosnia and Herzegovina to move forward.

Keywords: AKI, chronic hemodialysis, chronic renal failure, kidney transplantation, survival analysis

INTRODUCTION

It has now been more than two decades since the end of the 1992–95 war in Bosnia and Herzegovina. This may well be the proper time to provide the nephrology community with an appraisal of the care of patients with chronic kidney disease (CKD) in the pre-war, war and post-war periods in the European transitional country. Each of the periods described, even during war, had its specificities as well as its good and bad sides, as articulated by Norbert Lameire that 'in many cases war moves medical practices and innovation forward' [1]. In today's world, it is hard to find a peaceful nook without wars, socio-political turmoil, upheavals or natural catastrophes that affect human health and the ability to care for the needy. This report on

nephrology in Bosnia and Herzegovina draws attention to the hurdles faced for three turbulent years on that burdensome path of providing quality care, and the chance it offered in developing a successful transplant programme while facing the dreadful chaos of war and a migrant crisis.

HISTORICAL BACKGROUND

Impact on life in Yugoslavia

Bosnia and Herzegovina is a small and old country in the centre of the Balkans with a turbulent history, beginning as an independent kingdom in medieval times, through Ottoman and Austro-Hungarian occupation to becoming a part of Yugoslavia

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FIGURE 1: T.E. with PD nurse and other CAPD patient (2006).

T.E., born in 1975, from Vlasenica, Eastern Bosnia, who was, due to reflux nephropathy, commenced on HD when she was 9 years old, was transplanted at the Institute for Organ Transplantation in Sarajevo in 1986; the donor was her mother. Problems with thriving remained despite transplantation and she was not treated with growth hormone. Her final height was 150 cm. Up until 1992 she was on regular checkups in Sarajevo and her immunosuppression consisted of steroid, azathioprine and cyclosporine. At the beginning of the war, in 1992, she was displaced from her hometown and became a refugee in Zivinice, a small town near Tuzla, but did not come to our hospital for any further checkups. Due to blockades and general lack of medical supplies and drugs, she did not have enough immunosuppressive drugs and after some time, in October of 1994, she was admitted to our hospital with signs of overt uraemic syndrome. We put her back on HD and in 1998, she had HCV seroconversion, becoming HCV antibody positive. Due to exhausted vascular accesses, we switched her to CAPD. She did not have any other potential living kidney donor, and her chances of obtaining one from a deceased donor at that time were equal to zero. Unfortunately, she died in 2009 at the age of 34 years due to peritoneal membrane insufficiency, exhausted vascular accesses and catheter sepsis (Figure 1).



Preparation of water and solutions for HD was not an easy task during the war. It was extremely hard and expensive to deliver dialysis solutions in canisters via the hardly passable mountain paths that had to be used because other roads were blocked. In 1993, delivery of dialysis solutions to Tuzla had completely stopped. According to our agreement with Medecins du Monde, we tried and succeeded in producing dialysis solution in our hospital. Medecins du Monde provided the necessary chemicals, while we used the help of engineers from Tuzla's pre-war chemical industry. We utilized softened water from our water preparation facility. We assembled two plastic containers with a capacity of 1000 L each, and prochrom mixers were constructed. Containers would be filled with the exact amount of weighed chemicals and then softened water would be added in certain pre-defined proportions in order to obtain concentrated dialysis solution containing: Na 137 mmol/L, K 2.0 mmol/L, Ca 1.75 mmol/L, Mg 0.75 mmol/L, Cl 109 mmol/L, Na acetate 35 mmol/L and glucose 11.1 mmol/L. In order to produce 1000 L of concentrated dialysis solution, we would use $5.2 \, \text{kg}$ of KCl, $9 \, \text{kg}$ of $CaCl_2 \times 2H_2O$, $5.3 \, \text{kg}$ of $MgCl_2 \times 6H_2O$, $166.7 \, \text{kg}$ of Na acetate \times 3H₂O, 70 kg of glucose and 208.6 kg of NaCl. We were provided with NaCl from salt factory (Tuzla is a town that lies on salt stones/rocks and salty water). Filtrated solution would be poured into canisters pre-washed by softened water, and solutions would be chemically and microbiologically tested in the hospital laboratory and the factory's ionometer. Daily consumption of concentrated solution was 250 L, whereas monthly it was 7500 L. For around 9 months that we used our dialysis solution, we had neither electrolyte nor microbiological contamination. There were no microfiltres on dialysis machines.

after the First World War. During the Second World War, in 1943, Bosnia and Herzegovina became one of the six republics of the second Yugoslavia. The Communist period (1945-90) was different from that in the other countries of the Eastern Block. Yugoslavia was more liberal, more open towards the West, but still a country with a single-party communist system. One of the specificities of this period was the so-called workmen self-governance that in the end turned out to be economically inefficient, and the other was the so-called independence movement that made a positive political impact on life in Yugoslavia [2]. After dissolution of Yugoslavia at the beginning of the 1990s, an intensive and cruel war occurred in Bosnia and Herzegovina with huge civilian and military casualties. It is estimated that about 100 000 people were killed, another 300 000 wounded and 2 million became refugees during the period of 1992-95 [3].

The war ended in December 1995, with the signing of the Dayton Peace Accord, which brought peace but left the country with numerous structural, political and economic problems to surmount that continue to haunt the region. The Peace Accord structured Bosnia and Herzegovina into two entities and one district—a complicated political structure with heavy bureaucracy, such that there are 13 regional ministries of health without a common unifying national ministry.

Nephrology in Bosnia and Herzegovina in Yugoslavia (1945 - 92)

During the second Yugoslavian period, Bosnia and Herzegovina was one of the less developed economic regions of the country. The priorities of the health authorities were eradication of tuberculosis, typhoid, endemic lues, goiter, trachoma and scabies [4]. Nephrology emerged at the beginning of 1970s, with the establishment of dialysis centres (DCs) in the capital Sarajevo and in Tuzla. In 1974 and until 1992, Sarajevo had an Institute for Organ Transplantation that performed more than 200 living-related kidney transplantations (LRD). Nephrology in Tuzla developed because of its close proximity to the regions of Balkan Endemic Nephropathy (BEN) in Northeastern Bosnia. At that time, BEN was a mysterious disease that attracted the interest of foreign nephrologists [5]. Initial experiences in treating BEN patients by dialysis in Bosnia and Herzegovina were reported in 1972 [6]. Dialysis in Sarajevo and Tuzla has developed relatively fast, following new developments in the field (haemoperfusion in 1983, haemofiltration, biofiltration and plasmapheresis in 1986). Progress in clinical nephrology and immunology was slower. One area of progress was the study on early phases of BEN, with kidney biopsies performed with support from colleagues from Slovenia and Croatia [7-11] in 1986. Today, there is a general agreement on the multifactorial aetiology of BEN that develops in genetically predisposed individuals chronically exposed to a causative agent found within endemic areas (most likely aristolochic acid) [12].

War and the immediate post-war period (1992-96)

When the war started in April of 1992, the country was divided into three parts and all organized medical services were demolished. Communication and transportation to some parts of the country were completely blocked. A number of medical personnel left hospitals. Dialysis therapy for chronic and acute patients had to be reorganized. In May of 1993, we sent a letter through United Nations forces in Tuzla to the editorial board of Nephrology Dialysis Transplantation explaining the dire circumstances faced by our dialysis patients and begging for help. It is only after the war that we found out that the letter was actually

published in NDT [13]. In an earlier issue of the same volume, a paper by El-Reshaid et al. [14] reported the fate of chronic dialysis patients in Kuwait during its occupation by Iraq 1990-91. In the accompanying editorial written by Stewart Cameron, he states it is 'sad that such a paper can, or needs to, be written; but it is part of the destructive way our world still tries to solve its problems, and even more sadly we may expect further such data in the future' [15], as indeed we did in Tuzla.

As in all wars, civilian facilities were one of the main military targets. In Bosnia and Herzegovina (1992-95), Ruanda (1994) and Kosovo (1999), a huge portion of the innocent civilian population were primary war targets. Civilian victims from those wars, of well over a million, were far more than the military casualties. Blockades of humanitarian aid, destruction of hospitals, and terrorizing medical and other humanitarian workers were common phenomena [16]. A report from 1994 characterizes the Bosnian war as one against the public health of the country [17]. The combination of displacement, and deprivation of food, fuel and medicine, all significantly increased the death rates from any illness especially among vulnerable groups such as the elderly and the very young [17]. The article also highlights the organizational problem of healthcare presented by refugees. In some towns, they even outnumbered the domestic population. Tuberculosis was rampant (before the war, Bosnia and Herzegovina had the highest prevalence and incidence of tuberculosis). International committees of the Red Cross, World Health Organization, United Nations International Children's Emergency Fund and United Nations High Commissioner for Refugees provided substantial support to the disrupted healthcare throughout the country. During this period, healthcare in all parts of Bosnia and Herzegovina, regardless of which side of the war, was free and based on donated material and unpaid labour of medical staff.

Acute kidney injury during the war

Post-traumatic acute kidney injury (AKI) is rare except during wars and natural disasters. A systematic review of the quality of evidence for injury and rehabilitation interventions in humanitarian crises was published in 2015 [18]. Of the 46 papers that met the inclusion criteria, 63% were due to armed conflict, of which the Yugoslav Wars constituted the most studied in a crisis context. Fifty-nine percent of the studies were published since the year 2000. Unfortunately, only two studies were considered of high quality. How can one expect high-quality studies during war conditions or massive disasters, especially in nondeveloped or developing countries? During the Bosnian War, we had no opportunity for research, but we did record some data about our acute and chronic kidney patients.

We analysed data from 69 patients with AKI sustained during the war in Tuzla (Table 1) not including the later described outbrake of haemorrhagic fever with renal syndrome (HFRS) in 1995. Patients were dialysed in-centre, the only mode available in those years, using acetate dialysis, water processed with

Table 1. AKI in Tuzla during the war of 1992-95

Patients Average age, number (N) mean ± SD		Men, mean \pm SD	Women	Dialysed	
	(years)				
69	38.22 ± 14.14	58 (84.06)	11 (15.94%)	38 (55%)	
Aetiology (%)	HFRS	War trauma	Poisoning	Other	
	23 (33)	15 (22)	7 (10)	24 (35)	
Mortality (%)	Total	Surgery	Dialysed	Not dialysed	
	20 (29)	14 (71)	17 (45)	3 (9.7)	

Table 2. Mortality of the chronic HD patients in Tuzla during 1991-96

Year	1991	1992	1993	1994	1995	1996
HD patients	175	130	124	116	127	141
Average age (years)	48	49	47	46	46	45
Female HD patients (%)	95 (54.29)	69 (53.08)	56 (45.16)	59 (50.86)	72 (56.69)	75 (53.19)
Deaths (%)	18 (10.28)	38 (29.23)	52 (41.23)	31 (26.72)	17 (13.38)	23 (16.19)
Average weekly hours of HD	12	10	8	10	12	12
Weekly number of HD sessions	3	2–3	2	2–3	3	3

softeners and dialysis solutions prepared in the hospital. Average survival time between hospital admission and death was 9 days. The leading causes of death were sepsis and gastrointestinal bleeding. Mortality was higher in patients who required dialysis. All oliguric dialysed patients had two or more organ failures and mortality increased with the number of failed organs. In patients with four organ failures, mortality was 100%. There were no deaths among those with AKI only. We were a tertiary centre for dialysis that saw only selected cases that could not be treated in war hospitals, and that explains the small number of cases we have shown here.

Bosnia and Herzegovina is a known endemic region for HFRS. The first case was described in 1952, with large outbreaks in 1952, 1967, 1986 and during the war 1994-95. Sporadic cases were diagnosed every year [19]. In 1995 in Tuzla, more than 450 individuals, mostly soldiers, sustained HFRS. More than 90% of them developed AKI of variable severity with an overall mortality of <1%. Haemodialysis therapy was needed in six patients (5.26%).

During the autumn of 1993, we had more than 200 cases of mushrooms poisonings due to food shortages, including 50 very difficult cases that required haemoperfusion therapy. Eight patients died (4%, five adults and three children).

Chronic dialysis during the war

During wars, the care of wounded and acutely ill patients marginalizes that of residents with chronic diseases dependent on expensive forms of treatment like dialysis [1]. In this regard, the major difficulties in dialysis treatment we encountered during the war (1992-95) were lack of dialysis supplies, medications, diagnostics and food, lack of processed water for dialysis (using of untreated water), electricity blackouts, lack of fuel for patient transportation, military attacks and the added burden by refugees (31% of the total number of dialysis cases). We used donated chemicals and the expert help of engineers from Tuzla's pre-war chemical industry in the preparation of water and solutions for haemodialysis (HD). There was no reuse of dialysers.

Mortality of our dialysis patients increased from 10.28% to 41% during 1993 through 1994 (Table 2), but with the end of blockade and the help we got, the numbers improved in the following years. Out of a total of 813 patients, 161 died (30 refugees), of whom 35 were hepatitis B surface antigen (HBsAg) positive. The leading causes of death were hyperkalaemia (43/ 161 patients, or 26.71%), cerebrovascular incidents (36/161 patients, or 22.36%) and acute pulmonary oedema (28/161 patients, or 17.39%). The continuous ambulatory peritoneal dialysis (CAPD) programme, which we had started in 1989, was stopped because of a lack of peritoneal dialysis (PD) solution. Centres in Croatia had a similar experience with their chronic cases as 'dialysis patients are definitely a very vulnerable and imperiled group, and it is necessary to plan how to take care of them in special circumstances, not just during natural disasters but also in case of unfortunate and tragic wars' [20].

Humanitarian aid

During the war, and in the immediate post-war period, there was chronic shortage of medications and medical supplies. On 2 September 1992, we received the first shipment of supplies from Medecins du Monde, Pharmaciens Sans Frontieres and Medecins Sans Frontieres. Unfortunately, their help was suddenly terminated at the end of 1992 due to communication and transport blockade of the Tuzla region that lasted until the spring of 1994. For more than a year, nothing entered the town, not even dialysers. Nevertheless, with help from Medecins du Monde, we tried and succeeded in producing dialysis solution in our hospital.

Of immeasurable help was the donation of seven dialysis machines-five from the German Society for Dialysis and Transplantation and two from the Norwegian Church Aid. Additionally, shipments of drugs and other material were made by Western European countries and the rest of the world, which consisted mostly of products with expired dates. We used them all without obvious adverse reactions. We were delighted when we discovered a substantial amount of dialysis catheters in one of the shipments, monoluminal, doublelumen, complete sets for implantation of temporary and tunnelled lines, all with expired dates. We did not notice higher rates of central line infections with their use either. Significant numbers of acute and chronic patients survived thanks to those catheters.

In 1994, colleagues from Medecins du Monde visited DCs in Bosnia and Herzegovina. This organization was responsible for several programmes including one on haemodialysis, and their analysis was published as a Special Feature in NDT. 'These programs rely totally on humanitarian aid due to a complete lack of pharmaceutical supplies, the influx of displaced populations, and the closing of access routes' [21].

Help provided by Medecins du Monde and other humanitarian organizations ceased in the fall of 1997, when our government was asked to assume the responsibility of financing treatment of chronic dialysis patients. Using a loan from the World Bank (1.3 million dollars), devastated DCs were fixed and equipped.

Examples of humanitarian collaboration between doctors and civilians concerning dialysis patients, were common. Exchange of civilians that took place on borders of battlefields involved dialysis patients, and that was how two dialysis patients from Srebrenica ended up in Tuzla, in the middle of 1993, after almost 2 years of living and being dialysed in a hospital in Serbia. In the divided town of Mostar, both Muslim and Christian dialysis patients were dialysed in one DC situated in the Christian part of town. There were also opposite examples. In 1993, soldiers brought in an end-stage renal disease patient found on the battlefield. He was in very poor condition and never spoke. Among other things, we suspected aluminium encephalopathy but could not prove it. He lived in our hospital until the end of the war and died a few years after that.



FIGURE 2: Anti-HCV-positive patients in Tuzla DC 1997-2016. EPO, erythropoietin; DC, dialysis center.

Nephrology in Bosnia and Herzegovina in the post-war period (1996-2016)

The post-war period brought different kinds of problems. Besides the residual poor economic conditions resulting from the former Yugoslav economy, human and material casualties, massive migrations, exile of citizens, and poor understanding and managing of private market initiatives resulted in substantial difficulties in the administration of healthcare systems as well as in most services of the new government. The Society for Nephrology, Dialysis and Transplantation in Bosnia and Herzegovina was founded in 1997. In 2000, a Renal Registry was established and now regularly sends data to the ERA-EDTA Renal Registry. Unlike countries from Eastern and Central Europe, dialysis in former Yugoslavia was well developed and widely available to all citizens. In the post-socialist era, between 1990 and 1996, the number of DCs in Eastern Europe had increased by 56%, and the number of those performing PD by 296% [22]. Eight years later, most countries in Eastern and Central Europe met the European standard of renal replacement therapies (RRT), but with substantial differences between them [23]. In Bosnia and Herzegovina, all citizens with health insurance have access to free RRT, including transplantation, whereas for those not having insurance, the costs are paid by the government.

The incidence and prevalence of CKD are increasing, especially in developing and undeveloped countries. Thanks to a grant from the The International Society of Nephrology's Kidney Disease Data Center (ISN-KDDC), we were one of the 12 countries (ISN-KDDC) involved in the study of 'Chronic kidney disease and cardiovascular risk in six regions of the world (ISN-KDDC): a cross sectional study' of 75 058 individuals. After data analysis, it was concluded that prevalence of CKDs was high, 14.3% in the general and 36.1% in the high-risk population, and that it was more pronounced in countries with low and middle incomes [24,25], as in Bosnia and Herzegovina. Bosnia and Herzegovina still lack official data on the prevalence of CKD and a registry of kidney biopsies, but the total incidence and prevalence of RRT in our country have increased from 96 to 105.6 per million population (pmp) and 421.7 to 749.9 pmp, respectively, in the period of 14 years (2002-16). There is only one nephropathologist for the whole country.

The continuing problems encountered are illustrated by the flooding central and western parts of Bosnia and Herzegovina because of heavy rains in May of 2014. Two DCs were destroyed, and around 200 HD patients had to be assigned to other DCs, regardless of political boundaries. No lives were lost, despite the absence of official guidelines or action plans for the care of chronic or acute kidney patients in natural disasters or war in our country.

Hepatitis infections in dialysis patients

The hepatitis C virus (HCV) was discovered in 1989, but in 2-3 years before the war, the former Republic of Yugoslavia still did not have screening for hepatitis C. In 1997, when Medecins du Monde donated reagents, we detected 73% of anti-HCV-positive patients out of the 164 prevalent HD patients tested. During the war, dialysis patients, wounded soldiers and civilians were receiving transfusions of donated but untested blood, as well as imported donated units, of uncertain origin. Until the end of 1999, seroconversion in Tuzla's DC was common (10.1-19.1%), so that the prevalence of anti-HCV-positive patients rose to 85%. We established a separate anti-HCV-negative dialysis room, and tightened general hygiene until erythropoietin became available to 90% of chronic dialysis patients in 2000. In the years that followed, there has been a slow but steady decline in the prevalence and incidence of hepatitis C (Figure 2). Similar experiences were reported from Iraq [26]. Hepatitis B was not a significant problem during the war despite irregular vaccination of patients and staff. According to data from Bosnia and Herzegovina Renal Registry, there were 4.4% of HBsAg-positive patients in 2006, and 2% in 2016, while those numbers for anti-HCV positive were 16.3 and 6.5%, respectively. There were no human immunodeficiency virus-positive dialysis patients either before or after the war.

Kidney transplantation in Bosnia and Herzegovina

The success of transplant programmes differs significantly in each Balkan country, even between neighbouring regions within each country. For example, Croatia is among the leading countries in transplantation, Slovenia has a successful transplant programme that dates from former Yugoslavia times, whereas Bosnia and Herzegovina, Macedonia and Montenegro do not have successful transplant programmes. The Regional Health Development Centre that covers all the Balkans with headquarters in Croatia is a technical body of the South-Eastern European Health Network established in 2011 with a goal to help Balkan countries to improve organ donation and transplantation, to ensure adequate numbers of transplantations for their citizens and to prevent transplant tourism [26, 27]. Despite our attempts and help from professional societies in Europe and abroad, the number of transplantations in Bosnia and Herzegovina has not increased significantly. The most important reasons for the small number of kidney transplantations are: absence of a transplant programme and the waiting list at the state level, no appointed explantation hospitals, absence of educational programmes for physicians, hospitals and the public, deficient number of transplant coordinators and lack of audits of recognition of brain death, and general indifference of our government towards transplantation. In the pre-war period (1974-91), there were 200 transplantations (all LRD), during the war there were none, and in the post-war period (1999-2017) there were 209 LRD, 19 unrelated LD and 44 from deceased donors.

Education

The post-war period brought significant improvements in nephrology education compared with those of former Yugoslavia. In the absence of sufficient facilities, Bosnia and Herzegovina was forced to refer most of its complicated renal patients to centres of excellence in Ljubljana, Zagreb and Beograd. Fortunately, there were many educational grants from the USA, Western Europe and other countries. We took advantage of the excellent ISN programmes, so that two of our university clinical centres are part of the Sister Renal Centers Program and four young trainees completed ISN fellowships, which has also opened new doors for future chapters of nephrology in Bosnia and Herzegovina.

CONCLUSION

The perception of war and natural disasters is quite different, from the victim's point of view, from the standardized and wellarranged healthcare systems in the developed world. The guidelines, written in peace, are extremely useful but often hard to follow during natural disasters or barbarous wars. That is why publication on this topic and experience-sharing in all available ways is important in order to prevent unnecessary causalities and losses from happening in future in such circumstances. Despite the unquestionable destructive nature of the war, it was a catalyt for nephrology in Bosnia and Herzegovina to move forward.

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CONFLICT OF INTEREST STATEMENT

None declared.

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