

Etiology, Risk Factors and Outcome of 1003 Cases of Infective Endocarditis from a 33-year National Survey in the Slovak Republic: An increasing proportion of elderly patients

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Abstract

BACKGROUND: Infective endocarditis (IE) is still a significant cause of mortality in European hospitals, despite of the fact, that large nationwide studies were performed in last twenty years and pathogens are well known. The aim of the study was to assess risk factors, mortality, etiology and proportion of elderly patients within a longitudinal nation wide survey of infectious endocarditis in Slovakia.

PATIENTS AND METHODS: Etiology, risk factors and outcome of 1003 cases of infective endocarditis (IE) in Slovakia over the last 33 years have been assessed.

RESULTS: The majority of IE were caused by *Staphylococci* (28.3%), 15.6% were due to *Viridans streptococci*, 10% due to *Enterococci*, 8.2% by gram-negative bacteria, *Acinetobacter baumannii* and *Pseudomonas aeruginosa*, 3.7% by other organisms and 31.0% of all cases were culture negative. The following risk factors were recorded: age > 65 (36.8%), rheumatic fever (15.3%), dental surgery (8.7%), previous non-cardiological surgery (8.2%), neoplasia (8.1%), diabetes (7.8%), any endoscopy (8.5%) and dialysis (4.6%). All patients were treated with antimicrobials, 507 (51%) also with surgery. Survival rate at day 60 after diagnosis was 88.1% (n=883). Only age >65 (34.3% vs. 49.5%, $p=0.045$) and persistent bacteremia (with three or more positive blood cultures 15.7% vs. 34.5%, $p=0.001$) were significantly associated with higher attributable mortality. Concerning risk factors, etiology and therapeutic strategies, rheumatic fever and neoplasia showed decrease in tendency. Dental surgery and tonsillitis were less frequent as well (26.7% vs. 2%, $p<0.001$ and 16% vs. 1%, $p<0.001$). There was a significant shift in etiology after 1997: culture-negative endocarditis was surprisingly more frequently observed

in the 2007–2017 period than before and represented 10.7% of all cases in 1984–1990 in comparison to 25.1–25.6% in 2007–2010 and 2011–2017. *Staphylococci* decreased from 48% to 29.6% (2007–2017), but are still major pathogens. Persistent bacteremia (3 or more positive blood cultures 5.3% vs. 24.7%, $p < 0.001$) was less commonly observed within the 1st period (1984–1990) in comparison to 2007–2010. More patients in the 1st period (1984–1990) had embolization complications of IE than in the fifth and sixth period (2007–2017) (76 vs. 16.3% $p < 0.001$). CNS embolization decreased from 14% to less than 5% ($p < 0.003$). Attributable mortality was lower too (26.7% vs. 9.5%, $p < 0.001$) because of increased proportion of cardiac surgery in the treatment of IE in 2007–2017 in comparison to 1984–1990.

CONCLUSIONS: Study has showed significant shifts in etiology, risk factors and complications over the observed time periods in Slovakia.

INTRODUCTION

Infective endocarditis (IE) is still a significant cause of mortality in European hospitals, despite cardiac surgery was widely accepted for treatment of IE and some new antibiotic were introduced within the last 20 years against multiresistant gram-positive bacteria. Several national studies on IE have been performed in Europe (EU) within the last 20 years (Fernandez-Guerrero *et al.* 1995; Hoen *et al.* 1996; Delahaye *et al.* 1995). The etiology of infectious endocarditis originating in the community includes *viridans streptococci*, *Staphylococcus aureus* and the HACEK group (*Haemophilus spp.*, *Actinobacillus spp.*, *Eikenella spp.*, *Cardiobacterium spp.*, *Kingella spp.*), which are responsible for 70–80% of cases, with the increase of *Staphylococcus aureus* and coagulase-negative *Staphylococcus spp.* (CO-NS) (Cetinkaya *et al.* 2001; Krcmery *et al.* 2003; Hricak *et al.* 2007). Nosocomial IE is caused mainly by CO-NS *staphylococci* and *enterococci*, but gram-negative bacilli and *Candida spp.* are increasing (Krcmery *et al.* 2003; Hricak *et al.* 2007; Gasparovic *et al.* 2017). Substantial proportion is culture-negative, despite of improving diagnostic tools and techniques. Although there are numerous reports on etiology and risk factors from the USA, some EU countries and Turkey (Cetinkaya *et al.* 2001), no data from Central and Eastern Europe (CEE) have been available until 2003–2008 (Krcmery *et al.* 2003; Hricak *et al.* 2007; Togoda 2017). Non-invasive and medical strategies, intensive cardiosurgery, valve replacement surgery and heart transplantation in CEE within 1980–2000 were less developed in comparison to former Western Europe Region. Also intravenous drug use as a risk factor is less frequent in comparison to Western Europe and US. Both of this risk factors for IE may be probably associated with differences in etiology and outcome of IE in Slovakia in comparison to other Western European countries.

The aim of this study was to reassess the etiology, risk factor and outcome of infectious endocarditis – mainly mortality and embolization to CNS, in 34 Slovak hospitals over 30 years. We have aimed also to compare six periods – 1st (1984–1990), 2nd (1991–1997), where mainly remedial therapy of IE was used, the 3rd (1998–2001) when cardiosurgery was introduced as therapy of IE in Slovakia and expanded in the 4th period (2002–2006), 5th period (2007–2010) and 6th period (2011–2017); and to compare etiology and mortality in 2007–2017 to 1984–1990.

PATIENTS AND METHODS

A nation-wide prospective survey on etiology, risk factors and outcomes of infectious endocarditis in Slovakia (population about 5.5 million) with a simple protocol was performed between 1984–2017. Thirty-four hospitals participated in the study and 1003 cases of infectious endocarditis were reported. Duke's criteria (Durack *et al.* 1994) were used for inclusion criteria and as a definition of probable or definitive infectious endocarditis. Definitions of diagnosis and outcome were used according to criteria modified by Bayer (Bayer *et al.* 1994). Risk factors for mortality and comparison of etiology, risk factors and outcome of infectious endocarditis in 1984–1990, in 1991–1997, in 1998–2001, in 2002–2006, in 2007–2010 and 2011–2017 were compared. Differences between the groups of patients (cured vs. died/ 1st period – 1984–1990 vs. 6th period – 2007–2010) were assessed by univariate analysis. Chi-square test or t-test for trends were performed, computerized with the open source statistical package "R" and $p < 0.05$ was considered significant.

RESULTS

In total, 1003 cases of IE were reported from 34 hospitals over the last 33 years and 309 (31%) were culture-negative. Of the rest culture-positive cases, the most frequently isolated pathogens were *Staphylococci* (30.9%) including *S. aureus* and coagulase-negative *Staphylococci* (Co-NS). *Viridans streptococci* were diagnosed in 15.6%, *Enterococcus faecalis* in 10% and 8.2% were gram negative bacilli. In 501 cases the aortic valve and in 457 the mitral valve was infected. There were only 46 (<5%) cases of right side endocarditis. Men were more frequently infected (72.3%) than women. The most frequently identified risk factors were: age > 65 in 36.2%, rheumatic fever in 15.9%, dental procedure in 8.7%, neoplasia in 8.1% and prior surgery in 8.2%. All patients were treated with antimicrobials (average length of therapy was 29.5 days) and 507 (50.7%) also with surgery (valve replacement). One hundred twenty (11.9%) died and 883 survived at days 60 after diagnosis endocarditis was made. Average length of antibiotic treatment was 29.5 days (26.5 days for those who died and 30.5 days for survivors ($p < 0.05$). Average treatment was longer

Tab. 1. Risk factors and mortality of 1003 cases of infective endocarditis in 1984–2017

Risk Factors	All (899 cases)	1st period 1984–1990 (75 cases)	2nd period 1991–1997 (180 cases)	3rd period 1998–2001 (159 cases)	4th period 2002–2006 (190 cases)	5th period 2007–2010 (295 cases)	6th period 2011–2017 (103 cases)	1st vs. 5th period		
								RR	CI [95%]	p-value
Age>65	362 (36.2%)	25 33.30%	46 25.50%	56 35.20%	73 38.40%	120 40.70%	42 41.00%	1.5	-	0.045
Rheumatic fever	153 (10.3%)	30 40%	54 30%	28 17.60%	23 12.10%	13 4.40%	5 4.9%	5.2	3.7-7.2	0.001
Neoplasia	81 8.10%	16 21.30%	12 6.70%	12 7.50%	16 8.40%	19 6.40%	6 5.9%	2.6	1.7-3.9	0.001
Diabetes mel-litus	78 7.8%	4 5.30%	11 6.10%	20 12.60%	38 20%	2 0.70%	2 2.00%	3.4	1.9-6.2	0.02
I.v. drug abuse	17 1.7%	0	2 1.10%	1 0.60%	1 0.50%	11 3.70%	2 2.00%	-	-	-
Previous surgery noncardiac	82 8.2%	10 13.30%	14 7.80%	11 6.90%	25 13.20%	16 5.40%	6 5.9%	2	1.2-3.47	0.03
Endoscopy	85 8.5%	10 13.30%	8 4.40%	8 5%	23 12.10%	28 9.50%	8 7.9%	-	-	NS
Vitium cordis	59 5.9%	1 1.30%	6 3.30%	2 1.30%	12 6.30%	28 9.50%	10 9.9%	0.2	0.1-1.1	0.03
Dialysis	46 4.6%	4 5.30%	8 4.40%	14 8.80%	6 3.20%	10 3.40%	4 3.9%	-	-	NS
Dental surgery	87 8.7%	20 26.70%	37 20.50%	8 5%	15 7.90%	5 1.70%	2 2.00%	5	3.7-6.9	0.001
Tonsillitis	43 4.3%	12 16%	15 8.30%	3 1.90%	10 5.30%	2 0.68%	1 1.00%	4.8	3.5-6.6	0.001
Embolization	279 28.00%	57 76%	40 22.20%	85 53.50%	33 17.40%	48 16.30%	16 15.8%	8	4.9-12.9	0.001
CNS Embolisa-tion	86 8.6%	11 14.6%	14 7.8%	12 7.3%	24 11.8%	15 5.1%	5 4.9%	2	1.1-3.55	0.03
Etiology										
Viridians strep-tococci	156 15.60%	11 -14.70%	22 -12.20%	29 -18.20%	30 -15.80%	48 -16.30%	16 15.9%	-	-	NS
Staphylococci	309 30.9%	36 -48%	60 -33.30%	39 -24.50%	64 -33.70%	81 -27.50%	29 28.6%	2	1.3-3	0.001
Enterococci	100 10.00%	9 -12%	21 (11.7%)	4 -2.50%	12 -6.30%	39 -13.20%	15 14.7%	-	-	NS
Gram-negative bacteria	82 8.2%	8 -10.70%	18 -10%	11 -6.90%	23 -12.10%	16 -5.40%	6 5.9%	-	-	NS
Culture nega-tive IE	309 30.9%	8 -10.70%	50 -27.70%	88 -55.40%	63 -33.20%	74 -25.10%	26 25.9%	0.4	0.2-0.84	0.01
Persistant IE (3 and more posi-tive blood cul-ture)	184 18.4%	4 -5.30%	37 -20.50%	5 -3.10%	39 -20.50%	73 -24.70%	26 25.6%	0.2	0.08-0.6	0.001
Therapy and Outcome										
Pretreated with ATB for other dg.	403 40.3%	16 -21.30%	37 -20.50%	44 -27.70%	103 (54.2%)	148 (50.2%)	55 54.5	0.3	0.2-0.6	0.001
ATB only	496 49.6%	58 -77.30%	120 (66.7%)	75 -47.20%	95 -50%	112 -38%	37 35.5%	4	2.4-6.6	0.001
ATB+surgery	507 50.7%	17 -22.70%	60 -33.30%	84 -52.80%	97 -51.10%	183 -62%	66 65.3%	0.3	0.2-0.4	0.001
Mortality	120 12.00%	20 -26.70%	40 -22.20%	21 -13.20%	10 (5.3%)	29 -9.80%	10 9.9%	2.4	1.6-3.6	0.001

in staphylococcal and enterococcal IE (32–35 days), in comparison to culture-negative IE (28–32 days). Univariate analysis showed significant differences in some of the risk factors predicting mortality when comparing patients who survived and died: persistent bacteremia with three or more positive blood cultures (15.7% vs. 37.5%, $p < 0.001$), previous non-cardiac surgery (7.3 vs. 18.3%, $p = 0.003$), age < 65 (34.3% vs 49.6%, $p < 0.049$) and antibiotic therapy only (without surgery) (47.6% vs. 71.7%, $p < 0.001$). Absence of surgery was related to higher mortality and vice versa, antibiotic therapy plus surgery significantly improved outcome and reduced mortality ($p < 0.01$) (Table 1–2). Analyzing longitudinal trends in risk factors, etiology and outcomes of IE in six periods: 1984–1990 (75), from 1991–1997 (180 cases), from 1998–2001 (159 cases), from 2002–2006 (190 cases), 2007–2010 (295 cases) and 2011–2017 (103 cases): rheumatic fever showed decrease tendency, since prevalence of rheumatic risk factors in Slovakia is rapidly decreasing. Dental surgery and tonsillitis were less frequent as well (26.7% < 0.001). There was a significant shift in etiology between the first, second and fifth, sixth study period: culture-negative endocarditis (despite better bacteriological techniques) was more frequently observed in the 6th period than 1st period and represented 10.7% of all cases in 1984–1990 in comparison to 25.1% in 2007–2017. Staphylococci decreased from 48% to 28.6% (2007–2017). Persistent bacteremia (3 or more positive blood cultures 5.3% vs. 25.6%, $p < 0.001$) was less commonly observed in the 1st period (1984–1990) in comparison to 2007–2017. More patients in the 1st period (1984–1990) had embolization as a complication of IE than in the 5th period (2007–2010) (76 vs. 15.8%, $p < 0.001$) and 6th study period (2011–2017); however embolization to the CNS showed decreasing trend in the last period and was rare (4.9%).

DISCUSSION

Our previous two studies analyzed 336 and 606 cases of IE from Slovakia in a subseries. The etiology differed from both US (Bayer *et al.* 1994; Hoen *et al.* 1996) and European studies, where 60–70% viridans streptococci (Hoen *et al.* 1995; Delahaye *et al.* 1995) were diagnosed. We have seen much less viridans streptococci in etiology in comparison to USA and EU studies, with 50–70% streptococcal etiology and we have found only 15.6% viridans streptococci in the etiology of infectious endocarditis. This may be caused by the implementation of new guidelines for prevention of IE (1998) by Slovak Cardiology and Stomatology Society (Hricak *et al.* 1999; Slovak Society of Cardiology and Society of Stomatology 1999) focusing mainly on viridans streptococci as the commonest pathogens. Culture-negative IE increased in comparison to 1991–1997 despite improved diagnostic techniques, however subsequently decreased to 25.1% in 2007–2010 and 25.6% in 2007–2011. Probably because most microbiology laboratories

no longer wait for definitive results in “negative” blood cultures for 7–10 days and more after recommendations (Hricak *et al.* 1999; Slovak Society of Cardiology and Society of Stomatology 1999) of both Societies after 1990–2000. Some other nationally based studies showed 40–50% cases of IE where no etiology was obtained. Prophylaxis or empiric therapy used for undiagnosed or misdiagnosed cases of „fever“ may contribute to the increasing proportion of cultures negative endocarditis (Figure 1–2) and also high mortality in these subgroups.

A study on IE performed in Turkey in community with relatively high prevalence of rheumatic fever and 228 episodes of IE were reviewed. *S. aureus* and viridans streptococci were the most commonly isolated agents of native valve endocarditis. About 50% of all cases in this study were also culture-negative (Cetinkaya *et al.* 2001).

Proportion of endocarditis due to *Enterobacteriaceae*, *Pseudomonas aeruginosa* and *Acinetobacter spp.* was higher (8,5%) than in other national or longitudinal surveys (Cetinkaya *et al.* 2001; Hoen *et al.* 1995; Delahaye *et al.* 1995; Togoda 2017). It is not easy to explain this shift in etiology. The increase in cardiac surgery and lower intravenous drug addiction in our country in comparison to the other EU member states could contribute to this. Also implementation of new guidelines for prevention of IE (1998) by Slovak Cardiology and Stomatology Society focused mainly against viridans streptococci and staphylococci as the commonest pathogens probably contributed to the shift in etiology.

Although intravenous drug use in Slovakia is less common than in the USA or in Western Europe (there were about 1600 registered intravenous drug users and only 408 registered HIV positive individuals among 5.5 millions inhabitants of Slovakia (Yearbook of statistics 2011), staphylococci were the commonest organisms present in 30% of cases, which is similar to US studies (Hoen *et al.* 1995; Delahaye *et al.* 1995), but higher than Europe (Fernandez-Guerrero *et al.* 1995). Surprisingly, some well-known risk factors, such as dental surgery, endoscopy and catheters were less frequently observed. Previous endoscopy, surgery, vascular catheters, and dialysis were reported to be the risk factors in endocarditis cases in other studies (Krcmery *et al.* 2003; Hricak *et al.* 2007; Demitrovicova *et al.* 2007).

In regard to outcome, the duration of antibiotic therapy seems to be less important whereas the addition of early cardiac surgery to ATB therapy decreased significant mortality. In comparison to those treated only with antibiotics, death rate was lower in those who underwent cardiac surgery. However, overall mortality (13,5%) in comparison to other US or European studies (20–35%) was lower in our national survey. Culture-negative endocarditis (treated empirically) had outcome similar to culture positive endocarditis which was treated according to the culture results. One explanation for this phenomenon may be that initial (empiric) therapy used endocarditis in Slovakia within the last 10 years was mainly composed of an anti-Gram-positive agent (cefotaxim or ampicillin)

Tab. 2. Predictors of mortality in 1003 cases of infective endocarditis in 1984–2017

Risk Factors	All 1003 cases	Survived 779 cases	Death 1 1984–1990 20/75	Death 2 1991–2001 61/339	Death 3 2002–2006 10/190	Death 4 2007–2010 29/295	Death 5 2011–2017 10/103	Total death 130/1003 CI [95%]	Survived vs. Total Deaths		
									CI [95%]	p-value	
Age>65	362 (36.9%)	267 (34.3%)	8 (40%)	24 (39.3%)	4 (40%)	17 (59.3%)	4 (40%)	53 (44.2%)	-	0.89-1	0.049
Rheumatic fever	148 (16.5%)	122 (15.7%)	5 (25%)	16 (26.2%)	2 (20%)	3 (10.3%)	-	26 (21.7%)	-	-	NS
Neoplasia	75 (7.8%)	60 (7.7%)	3 (15%)	8 (13.1%)	1 (10%)	3 (10.3%)	-	15 (12.5%)	-	-	NS
Diabetes mellitus	75 (8.3%)	66 (8.5%)	2 (10%)	6 (9.8%)	1 (10%)	0 (0%)	-	9 (7.5%)	-	-	NS
I.v. drug abuse	5 (0.6%)	0 (0%)	1 (5%)	2 (3.3%)	0 (0%)	2 (6.8%)	-	5 (4.2%)	-	-	-
Previous noncardiac surgery	76 (8.5%)	57 (7.3%)	3 (15%)	8 (13.1%)	1 (10%)	7 (24.1%)	2 (20.1%)	21 (18.8%)	-	0.75-0.98	0.003
Endoscopy	77 (8.6%)	67 (8.6%)	2 (10%)	4 (6.6%)	1 (10%)	3 (10.3%)	-	10 (8.3%)	-	-	NS
Vitium cordis	49 (5.5%)	40 (5.1%)	2 (10%)	6 (9.8%)	1 (10%)	0 (0%)	-	9 (7.5%)	-	-	NS
Dialysis	49 (5.5%)	39 (5%)	2 (10%)	6 (9.8%)	1 (10%)	1 (3.3%)	-	10 (8.3%)	-	-	NS
Dental surgery	85 (9.7%)	77 (9.9%)	2 (10%)	4 (6.6%)	1 (10%)	1 (3.3%)	-	8 (6.6%)	-	-	NS
Tonsillitis	42 (4.7%)	35 (4.5%)	2 (10%)	4 (6.6%)	1 (10%)	0 (0%)	-	7 (5.8%)	-	-	NS
Embolisation	263 (29.3%)	223 (28.6%)	2 (10%)	35 (57.4%)	1 (10%)	2 (6.8%)	-	40 (33.3%)	-	-	NS
Etiology											
Viridians streptococci	156 (15.6%)	133 (17.1%)	1 (5%)	3 (4.9%)	0 (0%)	4 (13.7%)	-	7 (6.9%)	-	1.06-1.17	0.002
Staphylococci	283 (28.3%)	239 (30.7%)	9 (45%)	27 (44.3%)	5 (50%)	10 (34%)	3 (30%)	44 (36.3%)	-	-	NS
Enterococci	100 (10%)	71 (9.1%)	2 (10%)	5 (8.2%)	1 (10%)	6 (20.6%)	-	14 (12.7%)	-	-	NS
Gram-negative bacteria	82 (8.2%)	73 (9.4%)	0 (0%)	1 (1.6%)	0 (0%)	2 (6.8%)	1 (10%)	4 (2.5%)	-	1.05-1.18	0.019
Other	37 (3.7%)	32 (4.1%)	0 (0%)	2 (3.3%)	1 (10%)	3 (10.3%)	-	5 (4.2%)	-	-	NS
Culture negative IE	283 (28.3%)	247 (31.7%)	7 (35%)	22 (36.1%)	3 (30%)	4 (13.7%)	-	36 (30%)	-	-	NS
Persistent IE (3 and more positive blood culture)	160 (16.0%)	122 (15.7%)	5 (25%)	15 (24.6%)	3 (30%)	12 (40.8%)	2 (20%)	38 (34.5%)	-	0.8-0.95	0.001
Therapy and Outcomes											
ATB only	469 (49%)	374 (48%)	15 (75%)	52 (83.6%)	6 (60%)	13	9 (90%)	85 (71.1%)	-	0.82-0.91	0.001
ATB+surgery	507 (51%)	407 (52.3%)	6 (30%)	9 (14.8%)	4 (40%)	16	1 (10%)	35 (28.3%)	-	1.08-1.2	0.001
Average duration of therapy	29.5	30.5	27.5	28.8	25.4	24.6	20.9	24.5	-	-	NS

in combination with an aminoglycoside, which probably covered the majority of “classical” pathogens.

Within the last 20 years we observed a dramatic increase in cardiac surgery (from 828 cardiosurgical interventions to more than 6000 per year and from 1 to 4 centers in 2017) including the treatment of IE, which resulted in a trend towards reducing mortality due to IE (18% in 1991–1997 vs. 9.8% in 2007–2017). Although more clinical complications in IE occurred in the last period (such as embolization), lower mortality was noted because of better diagnosis and more cardiac surgical intervention that in past decade

Proportion of rheumatic fever as commonest factor in developing countries decreased from 40% in 1984 to 4.4% in 2007–2017 due to decreasing population with rheumatic fever patients in elderly population. Also proportion of previous non-cardiac surgical interventions among IE cases decreased within the entire period of 25 years, probably due to implementation of guidelines for prophylaxis of IE in 2003 in selected surgical interventions (from 13.3% to 5.4%). Preventive guidelines were adapted as well as in 2000 by Slovak Society of Cardiology and Stomatology possibly led also to decrease of prior dental surgery as a risk factor for IE since 1984–1990 (26.7%) to only about 2% in 2007–2017. In etiology of blood culture isolates was stable, staphylococci was leading cause during all 6 periods, from 1984 to 2010, following by viridans staphylococci and enterococci, proportion of culture negative cases decreased from 55.4% in 1998–2001 to 25.1% in 2007–2017 probably due to better microbiological techniques. Concerning therapy, proportion of persistent positive blood cultures remains relatively stable but embolization during bacteremia decreased from 53.5% (1998–2001) to 16.3% (2007–2010) due to increasing population of surgically treated IE cases (22.7% in 1984 to more than 66 % in 2007–2017) due to growing availability of cardiosurgical care. Concerning mortality, significant decrease of IE related deaths from 26.7% to about 10% was possibly related to increasing proportion of cardiac surgery (22.7 to 62%) and also number of available antibiotic (apart of linezolid) in comparison to 1990. When comparing 6 periods concerning outcome risk factors, no significant relationship between risk factors and attributable mortality was observed, but decreasing trends in mortality on staphylococcal IE have been observed (48% in 1984 to 27.5% in 2017). Same trends were observed in combination of surgical and ATB therapy in comparison to ATB therapy only. Combined therapy was associated with better outcome in comparison to remedial therapy without valve replacement. (Kacer *et al.* 2011; Gasparovic *et al.* 2017).

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