Enterococcal endocarditis in the beginning of the 21st century: analysis from the International Collaboration on Endocarditis-Prospective Cohort Study

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Abstract

Enterococci are reportedly the third most common group of endocarditis-causing pathogens but data on enterococcal infective endocarditis (IE) are limited. The aim of this study was to analyse the characteristics and prognostic factors of enterococcal IE within the International Collaboration on Endocarditis. In this multicentre, prospective observational cohort study of 4974 adults with definite IE recorded from June 2000 to September 2006, 500 patients had enterococcal IE. Their characteristics were described and compared with those of oral and group D streptococcal IE. Prognostic factors for enterococcal IE were analysed using multivariable Cox regression models. The patients' mean age was 65 years and 361/500 were male. Twenty-three per cent (117/500) of cases were healthcare related. Enterococcal IE were more frequent than oral and group D streptococcal IE in North America. The 1-year mortality rate was 28.9% (144/500). *E. faecalis* accounted for 90% (453/500) of enterococcal IE. Resistance to vancomycin was observed in 12 strains, eight of which were observed in North America, where they accounted for 10% (8/79) of enterococcal strains, and was more frequent in *E. faecium* than in *E. faecalis* (3/16 vs. 7/364 , p 0.01). Variables significantly associated with 1-year mortality were heart failure (HR 2.4, 95% CI 1.7—3.5, p <0.0001), stroke (HR 1.9, 95% CI 1.3—2.8, p 0.001) and age (HR 1.02 per 1-year increment, 95% CI 1.01—1.04, p 0.002). Surgery was not associated with better outcome. Enterococci are an important cause of IE, with a high mortality rate. Healthcare association and vancomycin resistance are common in particular in North America.

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Introduction

Enterococci are reportedly the third most common group of endocarditis-causing pathogens after streptococci and staphylococci. A few, relatively small, case series of enterococcal infective endocarditis (IE) have been published [1–9]. Based on these studies, the most distinctive features of enterococcal IE are that they more frequently affect elderly and prosthetic valve patients [3,5,8], and are more often nosocomially acquired than other forms of IE [2,7]. Nosocomial acquisition appears to worsen outcome. The mortality rate is intermediate to that of streptococcal and staphylococcal IE [1,2,4,8]. Patients with prosthetic valve enterococcal IE are more likely to develop intracardiac abscesses and less likely to have detectable vegetations on echocardiography than patients with native valve enterococcal IE [3]. In contrast, native and

prosthetic valve enterococcal IE do not appear to differ in rate of complications, need for surgery or mortality [1].

To date, all but two [4,6] of these case series were collected retrospectively and some are more than 20 years old [9]. The aim of this study was to analyse the current characteristics and prognostic factors of enterococcal IE within the International Collaboration on Endocarditis – Prospective Cohort Study (ICE-PCS), which forms the largest series of IE ever collected prospectively.

Methods

International Collaboration on Endocarditis – Prospective Cohort Study

Data from the ICE-PCS were used for this study. The background and inclusion criteria of this prospective, multicentre, international registry of IE have been reported previously [10,11]. Between June 2000 and September 2006, 4794 patients from 64 centres in 28 countries were enrolled. The ICE-PCS database is maintained at the Duke Clinical Research Institute, the coordinating centre for ICE studies. Informed consent (oral/written) was obtained from all patients according to local institutional review boards or ethics committee guidelines at all sites.

Patient selection and data collection

Patients were identified prospectively using site-specific procedures to ensure consecutive enrollment. Patients were enrolled in the ICE-PCS if they met criteria for possible or definite IE based on the modified Duke criteria [12]. Only patients with definite IE were included in the current study. To preserve the assumption of independence of observations, only the first episode of IE recorded for an individual patient was used in the analysis.

The method of data collection for the ICE-PCS has been previously reported [11]. Briefly, all sites used a standard case report form to collect data. It included 275 variables and was developed by the ICE according to standard definitions. Data were collected during the index hospitalization and then entered at the coordinating centre or by site investigators using an Internet-based data entry system. Microbial species identifications were performed locally in each medical centre according to its own procedures. All sites obtained information on 1-year survival through the civil registry office, medical records and/or patient contact when necessary.

Definitions and case groups

Definitions of the variables included in the ICE-PCS case report form have been previously reported [11].

Community-acquired IE was defined as IE diagnosed at the admission time (or within the first 48 h) in a patient who did not fulfill the criteria for healthcare-associated infection. Healthcare-associated IE was defined as nosocomial IE or non-nosocomial healthcare-associated IE. Nosocomial IE was defined as IE that developed in a patient who was hospitalized for more than 48 h before the onset of signs or symptoms consistent with IE. Non-nosocomial healthcare-associated IE was defined as IE diagnosed within 48 h of admission in an outpatient with extensive healthcare contact, as reflected by any of the following criteria: (i) receipt of intravenous therapy, wound care or specialized nursing care at home within the 30 days before the onset of IE; (ii) attendance at a hospital or haemodialysis clinic or receipt of intravenous chemotherapy within the 30 days before the onset of IE; (iii) hospitalization in an acute care hospital for 2 or more days in the 90 days before the onset of IE; or (iv) residence in a nursing home or long-term care facility.

In an effort to group centres with geographical and sociodemographic similarities, five meta-regions were defined as follows: North America, South America, Northern Europe, Southern Europe/Middle East/Africa and Australia/New Zealand/Asia (see supporting data).

The group of enterococcal IE included all cases of IE due to *E. faecalis*, *E. faecium*, *E. durans*, *E. avium*, *E. casseliflavus* or *E. gallinarum*, as well as enterococci that could not be further identified to the species level. For comparative analyses, we formed two additional groups of IE, oral streptococci IE and group D streptococci IE. Table 1 shows the list of organisms that are included in these two groups. We did this because enterococci, oral and group D streptococci all belong to the *Streptococcaceae* family.

TABLE 1. List of pathogens included in the three groups of pathogens used for comparative analysis

Enterococci	*N*	Oral streptococci	*N*	Group D streptococci	*N*
E. faecalis	453	*S. mitis*	79	*S. bovis*[a]	270
E. faecium	19	*S. mutans*	64	*S. gallolyticus*	17
E. durans	6	*S. oralis*	42	*S. equinus*	2
E. casseliflavus	2	*S. sanguis*	31	*S. pasteurianus*	1
E. gallinarum	1	*S. salivarius*	23	Group D NIS[b]	3
Enterococci NIS[b]	19	*S. gordonii*	12		
		S. anginosus	17		
		S. constellatus	5		
		S. intermedius	5		
		S. milleri group NIS[b]	4		
		S. acidominimus	7		
		S. parasanguis	1		
		S. viridans NIS[b]	533		
TOTAL	500		823		293

[a]*S. bovis*' refers to the results of species identification according to the former, outdated classification of group D streptococci.
[b]Not identified to species level.

Statistical analysis

Data are presented as mean (SD) for continuous variables and as percentages for categorical variables. Simple comparisons were made using Kruskal–Wallis, chi-squared or Fisher exact tests as appropriate.

Multivariable Cox regression analysis was used to identify factors associated with in-hospital mortality. The endpoint was the status (dead vs. alive) 1 year after discharge from hospital. The following variables were evaluated for their potential impact on prognosis: age, sex, ICE meta-regions, Charlson index, diabetes mellitus, cancer, haemodialysis, valve prosthesis before IE, nosocomial acquisition, heart failure (defined by NYHA class 3 or 4), stroke, development of at least one paravalvular complication, and cardiac surgery. The latter variable was assigned a time-dependent format, as recommended for assessing the impact of cardiac surgery on outcome [13]. For multivariable analysis, variables entered into the model were those with a p-value ≤ 0.05 in bivariable analysis. A stepwise variable selection was then performed, with an enter p-value of 0.05 and a remove p-value of 0.05. Two age- and sex-adjusted models were built up: one within the group of enterococcal IE to identify prognostic factors associated with this condition and one across the three pooled groups to assess the impact of enterococci vs. oral streptococci and vs. group D streptococci on IE prognosis.

For all tests, statistical significance was determined at the 0.05 level. All statistical analyses were performed using SAS software (version 9.2, SAS Institute, Cary, NC, USA).

Results

A total of 1616 patients with definite streptococcal or enterococcal IE were identified according to the selection criteria (Fig. 1). There were 500 cases of enterococcal IE (30.9%), 823 cases of oral streptococcal IE (51.0%) and 293 cases of group D streptococcal IE (18.1%). The distribution of species is shown in Table 1.

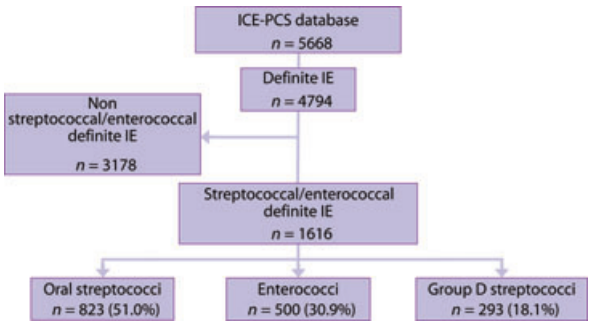

FIG. 1. Patients' selection flow-chart.

Of the 500 patients with enterococcal IE, 361 (72.6%) were male. The patients' mean age was 65.5 (15.3) years. The proportion of healthcare-associated IE was 117/500 (23.4%) (65/500 nosocomial and 52/500 non-nosocomial). Patients undergoing chronic haemodialysis accounted for 41/500 (8.4%). IE developed on native valves in 324/488 (66.4%) patients and on prosthetic valves in 142/488 (29.1%) patients. In the remaining 34 patients, the location of IE was either extravalvular or unknown. In terms of clinical manifestations, the only significant difference between *E. faecalis* and *E. faecium* IE consisted of a higher incidence of stroke in *E. faecalis* IE (16% vs. 0%, p 0.05). Two hundred and nine of the 497 patients (42.1%) underwent valve surgery during the initial hospital stay. Patients with prosthetic valve IE were less often operated on than patients with native valve IE (49/142 vs. 151/321, p 0.012). Non-operated patients were older than operated ones (68.5 vs. 62 years, p <0.001).

The 1-year mortality rate was 144/498 (28.9%), and higher in prosthetic valve IE than in native valve IE (55/142 vs. 80/322, p 0.002). The 1-year mortality rate did not differ between operated and non-operated patients in the overall enterococcal IE (56/219 vs. 88/278, p 0.14). Nor did it differ in native (32/144 vs. 48/177, p 0.3) or prosthetic (17/46 vs. 38/96, p 0.76) valve IE subgroups.

Overall, resistance to ampicillin and vancomycin was observed in 18 and 12 enterococcal strains, respectively. Seven of the 11 vancomycin-resistant strains were isolated from nosocomially-acquired IE, whereas this was the case for only 49/386 (13%) vancomycin-susceptible strains (p 0.004) (the place of acquisition was unknown or missing in one case of vancomycin-resistant IE and in 17 cases of vancomycin-susceptible IE). Eight of the 12 vancomycin-resistant strains (66.7%) were observed in North America, where they accounted for 10% of enterococcal strains. In contrast, no vancomycin resistance was observed in South Africa and Australia/New Zealand and the percentages of vancomycin resistance were only 1.0% (1/105 strains) in Northern Europe and 2.7% (3/111 strains) in Southern Europe/Middle East/Africa. The overall rate of high-level resistance to aminoglycoside was 111/290 (38%). It was lower in North America (12/54, 22%) than in the other four meta-regions (p 0.0002).

In addition, resistance to ampicillin and resistance to vancomycin were observed more often in *E. faecium* than in *E. faecalis* strains (9/16 vs. 8/404, p <0.0001 and 3/16 vs. 7/364, p 0.01, respectively). Resistance to aminoglycoside was not different between the two species. The 1-year mortality rate was higher in vancomycin-resistant than in vancomycin-susceptible enterococcal IE (7/12 vs. 110/384, p 0.03). Patients treated with an aminoglycoside-containing regimen presented

a lower 1-year mortality rate than patients treated without aminoglycoside (57/218 vs. 29/68, p 0.01).

The comparative characteristics of enterococcal, oral streptococcal and group D streptococcal IE are summarized in Fig. 2 and Table 2. Enterococcal IE were more common than oral and group D streptococcal IE in North America, where they accounted for 50.3% of the cases when pooling the three groups. In all four other meta-regions, the ranking was more conventional, with oral streptococci, enterococci and group D streptococci occurring in descending order (Fig. 2). Comparison of the three organism groups demonstrated the following characteristics of enterococcal IE. Enterococcal IE more often developed in relation to healthcare intervention and in elderly patients with co-morbid conditions, as exhibited by a higher proportion of patients with diabetes or receiving haemodialysis and by a higher Charlson index. Patients with enterococcal IE more often had a prior history of IE, a prosthetic valve or an implanted intracardiac device. The course of the disease did not differ significantly in terms of frequency and type of complications, although the time between first symptoms and admission was significantly shorter in enterococcal IE, which may reflect a more aggressive course of the disease and/or a more rapid diagnosis of healthcare-associated cases. The 1-year mortality rate was significantly higher for enterococcal than for streptococcal IE (Table 2).

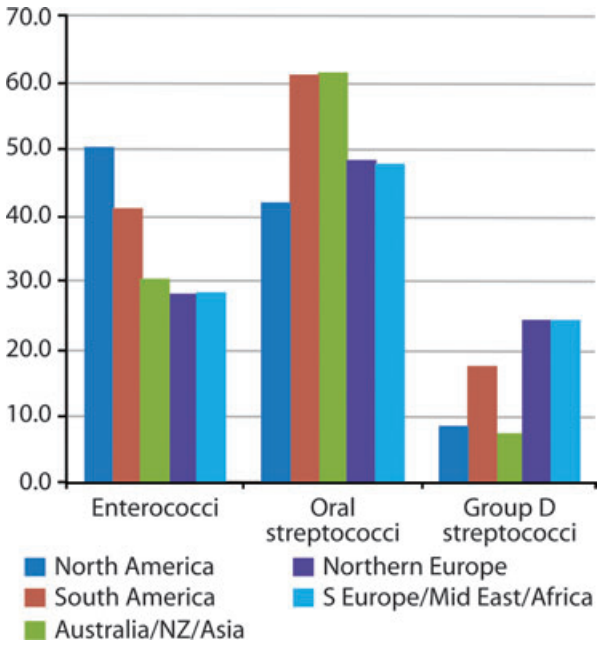

FIG. 2. Percentages of enterococci, oral streptococci and group D streptococci as the causative agents of IE among the five ICE meta-regions.

The variables that were analysed as potential prognostic factors for enterococcal IE are listed in Table 3. After bivariable analysis, six variables were then selected for the age- and sex-adjusted multivariable model. Finally, three variables were identified as significantly and independently associated with 1-year mortality. These were heart failure (HR 2.43 vs. no heart failure, 95% CI 1.71—3.45, p <0.0001), stroke (HR 1.90 time-dependent, 95% CI 1.28—2.82, p 0.001) and age (HR 1.02 per 1-year increment, 95% CI 1.01—1.04, p 0.002). Valve surgery, as a time-dependent variable, had no impact on prognosis. The same analyses were redone on the subgroup of *E. faecalis* IE and led to essentially the same results (i.e. the same prognostic factors were identified and associated with similar HRs (data not shown)).

In order to assess the role of enterococci as a potential prognostic factor, we built a multivariable model based on the pooled 1616 cases of IE. This model identified the same prognostic factors as in the previous step and three additional factors: diabetes, presence of a prosthetic valve before IE, and causative microorganism. The model thus demonstrated a significantly lower risk of death for oral streptococcal IE (HR 0.62, 95% CI 0.45—0.87) and group D streptococcal IE (HR 0.65, 95% CI 0.50–0.85), as compared with enterococcal IE (Table 4).

Discussion

This study confirms that *E. faecalis* accounts for about 90% of enterococcal IE, as previously reported [3]. Overall, enterococcal IE forms the third most important group of IE after streptococcal and staphylococcal IE. Interestingly, in this study, enterococcal IE was more frequent than both oral and group D streptococcal IE in North America, which may be related to the higher proportion of healthcare-associated IE in this part of the world [14], a hypothesis supported by the significantly higher rate of resistance to ampicillin and vancomycin for enterococci in North America as compared with the rest of the world. The present study also confirms that enterococcal IE is less often community acquired or involving native valves than previously reported. We actually found that among enterococcal IE, almost 25% were healthcare-associated IE, especially nosocomial, and 30% were prosthetic valve IE. In addition, enterococcal IE mainly affects elderly and debilitated patients. Interestingly, this newer profile was not associated with a higher rate of complications compared with oral or group D streptococcal IE. The in-hospital mortality rate of enterococcal IE, although significantly higher than in streptococcal IE despite a shorter delay to diagnosis, remained within the range of 11–18% observed in previous series [1,2,4]. In

TABLE 2. Main characteristics of enterococcal IE compared with those of oral and group D streptococcal IE

	Enterococci *n* = 500 30.9%	Oral streptococci *n* = 823 51.0%	Group D streptococci *n* = 293 18.1%	p value
Age (years), mean [SD]	65.5 (15.3)	54.6 (18.4)	65.2 (12.4)	<0.0001
Male sex, *N* (%)	361 (72.6)	584 (71.0)	218 (74.7)	0.46
History of IE, *N* (%)	62 (12.5)	86 (10.5)	21 (7.2)	0.07
Admission delay > 1 month, *N* (%)	172 (36.8)	350 (44.9)	142 (51.4)	<0.0001
Haemodialysis, *N* (%)	41 (8.4)	11 (1.4)	6 (2.1)	<0.0001
Diabetes, *N* (%)	110 (22.4)	90 (11.1)	56 (19.3)	<0.0001
Cancer, *N* (%)	55 (11.2)	67 (8.3)	34 (11.7)	0.11
Charlson index, mean [SD]	1.7 (1.8)	1.0 (1.5)	1.3 (1.5)	<0.0001
Place of acquisition, *N* (%)				<0.0001
Community	352 (70.4)	758 (92.1)	280 (95.6)	
Healthcare, nosocomial	65 (13.0)	12 (1.5)	3 (1.0)	
Healthcare, non-nosocomial	52 (10.4)	25 (3.0)	4 (1.4)	
Multiple, unknown, missing	31 (6.2)	28 (3.4)	6 (2.0)	
Intracardiac device, *N* (%)	61 (12.4)	31 (3.8)	21 (7.2)	<0.0001
Type of IE, *N* (%)				<0.0001
Native valve	324 (66.4)	641 (80.9)	216 (75.8)	
Prosthetic valve	142 (29.1)	130 (16.4)	62 (21.8)	
Other	22 (4.5)	21 (2.7)	7 (2.5)	
Location of vegetation, *N* (%)				0.18
Left-sided only	380 (80.3)	643 (83.0)	241 (87.6)	
Right-sided only	26 (5.5)	27 (3.5)	6 (2.2)	
Left + right	11 (2.3)	14 (1.8)	4 (1.5)	
Elsewhere	16 (3.4)	18 (2.3)	4 (1.5)	
No vegetation	40 (8.5)	73 (9.4)	20 (7.3)	
Missing information	27 (5.4)	48 (5.8)	18 (6.1)	
Stroke, *N* (%)	78 (16.0)	118 (14.7)	38 (13.3)	0.59
Embolic event, *N* (%)	94 (19.3)	147 (18.3)	70 (24.4)	0.08
Heart failure, *N* (%)	94 (18.8)	139 (16.9)	56 (19.1)	0.90
Intracardiac abscess, *N* (%)	57 (11.8)	110 (13.6)	33 (11.5)	0.51
Paravalvular complications in prosthetic valve IE, *N* (%)	53 (10.8)	41 (5.1)	15 (5.2)	0.0002
Valve surgery within 60 days, *N* (%)	209 (42.1)	380 (46.5)	137 (47.2)	0.22
One-year mortality, *N* (%)	144 (28.9)	120 (14.6)	52 (17.8)	<0.0001

IE, infective endocarditis.
Percentages are based on the missing data.

TABLE 3. Results of prognosis analysis by Cox regression analysis within the group of enterococcal IE. The multivariable model is adjusted for age and sex. The endpoint is 1-year mortality

	Bivariable analysis		Multivariable analysis	
	HR	95% CI	HR	95% CI
Age, per 1-year increment	**1.02**	**1.01–1.03**	**1.02**	**1.01–1.04**
Sex, male vs. female	0.72	0.49–1.07	–	–
Charlson index, per 1-unit increment	**1.29**	**1.11–1.50**	–	–
Haemodialysis, yes vs. no	1.15	0.65–2.04	–	–
Diabetes, yes vs. no	1.37	0.95–1.98	–	–
Cancer, yes vs. no	**1.62**	**1.04–2.53**	–	–
Nosocomial acquisition, yes vs. no	0.86	0.53–1.42	–	–
Stroke (time-dependent)	**2.00**	**1.36–2.94**	**1.90**	**1.28–2.82**
Heart failure, yes vs. no	**2.47**	**1.75–3.50**	**2.43**	**1.71–3.45**
Paravalvular complications	**1.48**	**1.06–2.06**	–	–
Surgery (time-dependent)	1.04	0.74–1.46	–	–

The variables selected as psoguotic factors are shown in bold.

TABLE 4. Identification of prognostic factors by Cox regression analysis in the pooled three groups of IE. The multivariable model is adjusted for age and sex. The endpoint is 1-year mortality

	Bivariable analysis		Multivariable analysis	
	HR	95% CI	HR	95% CI
Age, per 1-year increment	**1.03**	**1.02–1.04**	**1.02**	**1.01–1.03**
Sex, male vs. female	0.95	0.74–1.22	–	–
Charlson index, per 1-unit increment	**1.42**	**1.27–1.57**	–	–
Haemodialysis, yes vs. no	**1.91**	**1.20–3.03**	–	–
Diabetes, yes vs. no	**1.63**	**1.25–2.12**	**1.43**	**1.09–1.88**
Cancer, yes vs. no	**1.94**	**1.44–2.62**	–	–
Valve prosthesis before IE, yes vs. no	**1.82**	**1.44–2.29**	–	–
Nosocomial acquisition, yes vs. no	1.52	1.00–2.33	–	–
Stroke (time-dependent)	**2.31**	**1.78–2.99**	**2.23**	**1.71–2.91**
Heart failure, yes vs. no	**2.88**	**2.29–3.63**	**2.77**	**2.15–3.57**
Paravalvular complications	**1.71**	**1.37–2.14**	–	–
Surgery (time-dependent)	1.07	0.85–1.35	–	–
Causative microorganism				
Enterococci	1	–	1	–
Oral streptococci	**0.46**	**0.36–0.58**	**0.62**	**0.45–0.87**
Group D streptococci	**0.54**	**0.39–0.74**	**0.65**	**0.50–0.85**

The variables selected as psoguotic factors are shown in bold.

terms of prognosis, we failed to identify any factors specific to enterococcal IE, whose prognosis was mainly affected by age, occurrence of stroke and heart failure. However, we found that *Enterococcus* as the cause of IE was an adverse independent prognostic factor for mortality within the group of IE due to *Streptococcaceae*. In addition, after integration into the model of the 1471 cases of *Staphylococcus aureus* IE contained in the ICE-PCS database (data not shown), we found that *Staphylococcus aureus* as the cause of IE was associated with a higher risk of death (HR 1.6, 95% CI 1.3—2), which confirmed the lower risk of death associated with oral and group D streptococci.

The major strength of this study is that it assembled the largest series of prospectively collected cases of enterococcal IE ever published. Cases were collected recently and rapidly

(the first 6 years of the 21st century), providing an accurate view of the current profile of this disease.

A limitation of our study is the fact that case collection was tertiary care centre-based and not population-based. This may have introduced a referral bias towards a selection of more severe cases than the 'average'. However, in a large prospective population-based study of IE conducted recently, where enterococcal IE represented 10.5% (n = 52) of the 497 cases of IE collected, enterococcal IE was the third most frequent group of IE, occurred more frequently in patients with prosthetic valves, and was more prone to be nosocomially acquired than oral or group D streptococcal IE [15]. Therefore we can reasonably assume that this ICE-PCS series is representative of enterococcal IE in clinical practice. Another limitation is the fact that the impact of the antibiotic regimens on prognosis could not be analysed because the ICE-PCS database contains few details about the treatment: overall planned duration and predominant antibiotics used. Furthermore, this information was missing in about half of the study population, which could bias results. Finally, bacteriological identification techniques were not standardized because each centre used its own procedures. This explains the high rate of 'viridans' streptococci.

Enterococcal infection is an increasingly important cause of IE with a high mortality rate. Those affected include the elderly and patients with prosthetic valves or intracardiac devices. Healthcare association is common, in particular in North America, where emerging resistance to vancomycin is a matter of concern.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Distribution of centres by countries and meta-regions in the ICE-PCS.

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