Virulence of beta-hemolytic streptococci in infective endocarditis

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Abstract

Background Streptococci involved in infective endocarditis (IE) primarily comprise alpha- or non-hemolytic streptococci (ANHS). Moreover, beta-hemolytic streptococci (BHS) can be involved, and guidelines recommend the addition of gentamicin for the first 2 weeks of treatment and the consideration of early surgery in such cases. This study compared the morbidity and mortality associated with IE depending on the microorganisms involved (BHS, ANHS, staphylococci and enterococci).

Methods We conducted a retrospective observational study between 2012 and 2017 in a single hospital in France. The endpoints were overall in-hospital mortality, 1-year mortality and the occurrence of complications.

Results We analyzed 316 episodes of definite IE including 150 (38%), 96 (25%), 46 (12%) and 24 cases (6%) of staphylococcal, ANHS, enterococcal and BHS IE, respectively. In-hospital mortality was significantly higher in the staphylococcal ($n = 40$; 26.7%) and BHS groups ($n = 6$; 25.0%) than in the ANHS ($n = 9$; 9.4%) and enterococcal groups ($n = 5$; 10.9%) (all $p < 0.01$). The rates of septic shock and cerebral emboli were also higher in the BHS group than in the ANHS group [$n = 7$ (29.2%) vs. $n = 3$ (3.1%), $p < 0.001$; $n = 7$ (29.2%) vs. $n = 12$ (12.5%); $p = 0.05$, respectively].

Conclusion This study confirmed that BHS IE has a more severe prognosis than ANHS IE. The virulence of BHS may be similar to that of staphylococci, justifying increased monitoring of these patients and more ‘aggressive’ treatments such as early surgery.

Keywords

Infective endocarditis; streptococci; beta-hemolytic; virulence; cardiac surgery

Introduction

Streptococci, which have long been implicated in most cases of infective endocarditis (IE), have become the second most involved microorganisms after staphylococci [1,2]. This may be related to the generalization of antibiotic prophylaxis in high-risk patients during specific dental procedures [2] and to the increased rate of nosocomial infections in elderly populations [3].

Alpha-hemolytic and non-hemolytic streptococci (ANHS) account for most of the streptococci involved in IE [4], whether their presumed origin is oral (*mitis-oralis* group) or gastrointestinal (*bovis* group). IE due to beta-hemolytic streptococci (BHS) is relatively rare, and its management has not been clearly defined [5]. Considering the high virulence of group B, C and G streptococci, recent guidelines recommend the addition of gentamicin for the first 2 weeks of treatment despite a low level of evidence [5,6].

Thus, this study aimed to compare the characteristics of IE depending on the microorganisms involved, focusing on the mortality and morbidity associated with ANHS and BHS infections.

Methods

Study design

This retrospective study was conducted in the Strasbourg University Hospital, which is considered to be a reference center for the management of IE for a large region in France with approximately 70 cases per year. Data were extracted from a centralized database that stores medical information and therapeutic decisions of all patients with a final diagnosis of IE. Matrix-assisted laser desorption ionization-time of flight mass spectrometry was used determining the causative species.

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All patients diagnosed with definite IE according to modified Duke's criteria, in line with the 2015 European Society of Cardiology guidelines [5], involving staphylococci, streptococci or enterococci between January 2012 and December 2017, were included. Patients with pneumococcal IE and those with IE due to more than one microorganism were excluded. Patients aged less than 18 years and those with ventricular assist devices were also excluded. The primary endpoint of the study was overall in-hospital mortality rate. The secondary endpoints were the 1-year mortality rate occurrence of complications (septic shock, heart failure and stroke).

Definitions

The ANHS group included *S. bovis* complex, *S. mitis* complex, *S. mutans* complex, nutritionally variant streptococci (*Abiotrophia* and *Granulicatella*) and other non-classifiable non-BHS. The BHS group included *S. agalactiae* complex, *S. dysgalactiae* complex, *S. pyogenes* complex and *S. anginosus* complex, considering these latter as capable of beta-hemolysis and in line with the 2015 European Society of Cardiology guidelines [5]. The duration of antibiotic therapy was defined as the duration of appropriate treatment, in accordance with guidelines [5]. Septic shock was defined as a serum lactate level >2 mmol/L and the requirement for a vasopressor to maintain a mean arterial pressure ≥ 65 mmHg, in accordance with the Sepsis-3 definition [7]. Time to surgery was defined as the time from the day of definite diagnosis of IE (first day when a 'definite diagnosis' according to modified Duke's criteria was met) to the day of the surgical procedure. Late surgery (surgery after the end of antibiotic therapy) was excluded from this definition. Time to diagnosis was defined as the time from the day (actual or presumed) from symptom onset to the day of definite diagnosis. Previous heart disease was defined as any type of heart disease, including valvular heart disease.

Statistical methods

The descriptive analysis of continuous data was performed by obtaining the location parameters (i.e., mean, median, minimum, maximum, first and third quartiles) and the dispersion parameters (i.e., variance, standard deviation, range, interquartile range) for each variable. The Gaussian distribution of the data was tested using the Shapiro–Wilk test and quantile–quantile plots. The categorical data were described by obtaining the numbers and proportions for each category in the sample. Whenever useful, cross-tabulations were produced for each box of the table, which included numbers and proportions by row and column, as well as relative to the total. The inferential analysis for the categorical data was performed using the χ^2 test or Fisher’s exact test, depending on the theoretical size of the samples. Continuous data were compared using Student’s *t*-test (Gaussian distribution of the variable) or a non-parametric test in the opposite case (Mann–Whitney *U* test). Analysis of variance was used for continuous variables. The analyses were performed using R software version 3.4.3.

Ethical statements

This study was approved by the Ethics Committee of Strasbourg University Hospital (registration number: FC/dossier 2017-36). According to French legislation (Jardé law, N°2016-800), the non-opposition of all patients was sought.

Results

Study population

During the study period, 316 of 391 IE cases (81%) in the database fulfilled the inclusion criteria, including 150 (38.4%), 120 (30.7%) and 46 cases (11.8%) due to staphylococci, streptococci and enterococci, respectively (*Fig. 1*). Regarding streptococcal IE, 96 cases

(80%) involved ANHS, and 24 cases (20%) involved BHS. Most ANHS IE involved streptococci of the *S. bovis* (42 cases) or *S. mitis* group (41 cases). Over half of the BHS IE cases involved the *S. agalactiae* group (13 cases). More details on streptococcal species are available in the supplementary material (*Supplementary Table S1*).

The characteristics of patients are provided in Tables 1 and 2. The mean patient age was 65.8 $\pm$ 15.5 years and 223 patients were male (70.6%). Personal history and risk factors were comparable between the different microorganisms with the exception of intravenous drug users, who were overrepresented in the staphylococcal IE group.

Involvement of the aortic valve was most common (183 cases; 57.9%). This valve was affected more frequently in the ANHS and enterococci groups than in the BHS and staphylococci groups ($p < 0.01$). Overall, native valve IE was reported in 221 cases (69.9%), followed by bioprosthetic valve IE (71 cases; 22.5%) and mechanical valve IE (24 cases; 7.6%).

The number of positive blood culture bottles was significantly higher in the ANHS group than in the BHS group (3.0 vs. 1.9, $p < 0.0001$). The mean serum C-reactive protein and median serum troponin levels were also significantly higher in the ANHS group than in the BHS group (208 mg/L vs. 110 mg/L, $p < 0.0001$; 0.44 μ g/L vs. 0.07 μ g/L, $p = 0.01$).

In comparison with the BHS group data, echocardiographic findings revealed significantly more valvular perforations in the ANHS group (42 cases [43.8%] vs. 4 cases [16.7%], $p < 0.01$) and more cases of severe or important valve insufficiencies (54 cases [56.3%] vs. 7 cases [29.2%], $p < 0.001$). The frequency of cerebral embolism did not differ significantly between the microorganisms, although cerebral ischemia was numerically more frequent in the BHS groups than in the ANHS groups (11 cases [61.1%] vs. 26 cases [37.7%], $p = 0.08$).

134 Surgery rates were significantly different among the four groups, with lower rates in the
135 staphylococci and BHS groups, but the difference was not statistically significant between the
136 BHS and ANHS groups (11 cases [45.8%] vs. 61 cases [63.5%], $p = 0.11$). Similar results
137 were found regarding the duration of antibiotic therapy. Time to surgery and the length of in-
138 hospital stay did not differ significantly between the two groups. Time to diagnosis was
139 shorter in the BHS group than in the ANHS group (17.7 days vs. 36.5 days, $p < 0.01$). There
140 was no difference regarding the use of aminoglycosides.

141 Outcomes

142 The in-hospital mortality rates were significantly higher in the staphylococci and BHS groups
143 than in the ANHS and enterococci groups (26.7 and 25.0%, respectively, vs. 9.4 and 10.9%,
144 respectively; all $p < 0.01$), although the difference did not reach significance between the
145 BHS and ANHS groups (odds ratio [OR] = 3.18, 95% confidence interval [CI] = 0.82–11.56,
146 $p = 0.08$) (Table 3). This difference persisted after 1 year of follow-up. Among the six deaths
147 in the BHS group, five occurred in patients with *S. agalactiae* IE (mortality rate = 38.5% in
148 this subgroup).

149 In comparison with the findings for the ANHS group, IE involving BHS was complicated
150 significantly more often with septic shock (7 cases [29.2%] vs. 3 cases [3.1%], OR = 12.35,
151 95% CI = 2.52–81.33, $p < 0.001$). Heart failure and stroke rates were also higher in the BHS
152 group, but these differences did not reach statistical significance.

153 Discussion

154 Our study revealed major differences between streptococci IE according to whether they are
155 beta-hemolytic. The in-hospital mortality rate was higher in the BHS IE group than in the
156 ANHS IE group, albeit without significance, whereas mortality rates were similar between the
157 BHS and staphylococci groups. *S. agalactiae* group (former known as Group B streptococci)

158 was the predominant microorganism among BHS, as previously described [8,9]. This species
159 was involved in five of six deaths in this group. Previous data found that the mortality rates in
160 invasive BHS infections ranged from 11 to 21% [10–12] and from 25 to 27% in the largest
161 BHS endocarditis series [9,13]. *S. agalactiae* IE appears to have the worse prognosis, with
162 mortality rates of approximately 50% [14,15]. Ivanova-Georgieva et al. recently compared *S.*
163 *aureus* and *S. agalactiae* left-sided endocarditis and recorded similarly high mortality rates
164 [16].

165 More complications occurred in the BHS group than in the ANHS group, and septic shock
166 rates (29%) were similar to those reported for staphylococcal IE and higher than previously
167 reported findings [13,16]. Heart failure and stroke rates did not differ significantly between
168 the groups, but these conditions were more frequent in the BHS IE group. Cerebral ischemia
169 was observed in 61% of patients with BHS IE, which can be linked to the higher clinically
170 relevant stroke rate in this group. Nevertheless, the rate of heart failure in the BHS IE group
171 was surprising given the echocardiographic findings. Indeed, important or severe valve
172 insufficiency and valvular perforation were significantly less frequent in the BHS group than
173 in the other groups. Olmos et al. reported in 2015 high rates of valve insufficiency in 181
174 cases of *S. bovis* and viridans group streptococci IE [17]. We hypothesize that the longer time
175 to diagnosis after the onset of symptoms in the ANHS IE group than in the BHS or
176 staphylococcal IE group, as recently described [18], could have resulted in more valve
177 damage at the time of diagnosis. The increased frequency of damage in the ANHS IE group
178 could also be one explanation for the higher rate of surgery in this group, whereas the high
179 rate of complications in the BHS IE group might have delayed surgery because of the elevated
180 risk of perioperative death.

181 Most cases of BHS IE occurred in patients with apparently normal native valves, as only 33%
182 of patients had known heart disease and few patients had prosthetic valves (16.7%), although

these differences were not significant. Conversely, it appeared that ANHS IE occurred predominantly with a disposition to previous valvulopathy [17] relative to BHS IE [8]. This observation highlights the higher virulence of BHS than of ANHS. The more frequent involvement of the aortic valve in ANHS IE could be explained by the greater multivalvular involvement in this group (13 cases vs. none in the BHS group) and higher frequency of prosthetic valve IE (mitral prosthetic valve IE is less common than aortic valve IE [19,20]).

The average number of positive blood culture bottles differed according to the causative microorganism. The higher number of positive bottles was expected for staphylococci considering their virulence and the difficulty of sterilizing these samples. We believe that the difference observed between BHS and ANHS is linked to the time to diagnosis. Indeed, the diagnosis was made almost twice as early for BHS compared to ANHS, probably because of their more severe initial presentation.

Our study revealed a high proportion of patients receiving a combination therapy including aminoglycosides, especially in the streptococci groups. European and American guidelines for IE have recommended the adjunction of gentamicin for two weeks in BHS IE [5,6]. Some authors recently proposed to abandon this recommendation in native valve IE given the lack of evidence [21].

The present study was characterized by several strengths. Few data are available regarding BHS endocarditis, and this study analyzed a large cohort to assess the virulence of streptococci whether they were beta-hemolytic. In addition, our selection criteria were strict—we only included ‘definite IE’—and patients characteristics were consistent with the generally observed epidemiology of IE in large cohort studies [4,22].

This work also had limitations. The observational and retrospective design may be the source of biases inherent to this type of study. It was a single-center study; as such, the results might

reflect some local habits, and they must be generalized with caution. Finally, the data are limited by the rarity of BHS IE. As a result, our study lacks statistical power to demonstrate small differences, which may explain why the primary outcome did not reach statistical significance. We did not observe any *Streptococcus pyogenes* IE in our BHS group. This bacterium is rarely involved in IE and most reported cases are in children [23,24], but only adults were included in our study. We did not collect time-to-positivity of blood cultures.

In conclusion, BHS IE presented mostly as acute infections involving native and normal valves with more severe complications such as cerebral embolism or septic shock and high mortality rates. It appears that the virulence of BHS IE was similar to that of staphylococci, as recently reported [16]. Surgery has been correlated with improved survival [25]. The guidelines established in 2015 by the European Society of Cardiology recommend early surgery in patients with *S. aureus* prosthetic valve IE and when favorable early response to antibiotics is not achieved in patients with *S. aureus* native valve IE [5]. Thus, as suggested in the guidelines, this study provides additional arguments in favor of proactive management of BHS endocarditis.

Conflict of interests There are no reported conflicts of interest.

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Author's contribution YR, XA and YH designed the study. YR, XA, YH, AM, NL, ND and JPM collected the data. YR and XA analyzed the data. PR analyzed the microbiological data. YR performed the statistical analysis. YR and XA wrote the manuscript. All authors reviewed, revised and approved the final report.

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Fig. 1 Study flow chart

Abbreviations: IE, infective endocarditis; ANHS, alpha- or non-hemolytic streptococci; BHS, beta-hemolytic streptococci

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312 **Table 1** Demographic characteristics and valve involvement among 316 patients with IE according to the causative microorganism

	Total	Staphylococci	BHS	ANHS	Enterococci	<i>p</i>
	(<i>n</i> = 316)	(<i>n</i> = 150)	(<i>n</i> = 24)	(<i>n</i> = 96)	(<i>n</i> = 46)	
Age (years)	65.8 ± 15.5	63.9 ± 16.9	68.2 ± 14.0	66.1 ± 13.8	69,7 ± 13.8	0.13
Male gender	223 (70.6%)	105 (70.0%)	13 (54.2%)	69 (71.9%)	36 (78.3%)	0.21
<i>History and risk factors</i>						
Intravenous drug user	28 (8.9%)	22 (14.7%)	0	2 (2.1%)	4 (8.7%)	<0.01
Diabetes mellitus	90 (28.5%)	42 (28.0%)	7 (29.2%)	27 (28.1%)	14 (30.4%)	0.99
Immunosuppression	50 (15.8%)	29 (20.3%)	4 (18.2%)	13 (14.1%)	4 (8.7%)	0.33
Chronic renal failure	52 (16.5%)	24 (16.0%)	2 (8.3%)	16 (16.7%)	10 (21.7%)	0.57
Malignancy (including hematological malignancy)	73 (23.1%)	37 (24.7%)	6 (25.0%)	22 (22.9%)	8 (17.4%)	0.78
Previous heart disease	135 (42.7%)	59 (39.3%)	8 (33.3%)	50 (52.1%)	18 (39.1%)	0.15
<i>Valve(s) involved</i>						
Aortic†	183 (57.9%)	72 (48.0%)	12 (50.0%)†	69 (71.9%)†	30 (65.2%)	<0.01
Mitral	117 (37.0%)	57 (38.0%)	9 (37.5%)	33 (34.4%)	18 (39.1%)	0.93
Right-side	30 (9.5%)	21 (14.0%)	2 (8.3%)	6 (6.3%)	1 (2.2%)	0.054
≥2 valves involved	34 (10.8%)	16 (10.7%)	0	13 (13.5%)	5 (10.9%)	0.28
Intracardiac device infection	30 (9.5%)	22 (14.7%)	1 (4.2%)	5 (5.2%)	2 (4.3%)	0.04

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Type of valve							0313
Native	221 (69.9%)	111 (74.0%)	20 (83.3%)	65 (67.7%)	25 (54.3%)	314	
Prosthetic	95 (30.1%)	39 (26.0%)	4 (16.7%)	31 (32.3%)	21 (45.7%)		
Bioprosthetic valve (including TAVR)	71 (22.5%)	28 (18.7%)	3 (12.5%)	23 (24.0%)	17 (37.0%)	315	
Mechanical valve	24 (7.6%)	11 (7.3%)	1 (4.2%)	8 (8.3%)	4 (8.7%)	316	

Values are presented as n (%) or the mean ± standard deviation, as appropriate.

† $p < 0.05$ for the comparison between BHS and ANHS

Abbreviations: IE, infective endocarditis; BHS, beta-hemolytic streptococci; ANHS, alpha- or non-hemolytic streptococci; TAVR, transcatheter aortic valve replacement

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Table 2 Biological and echocardiographic findings, embolic events and management of 316 patients with IE according to the causative microorganism

	Total (<i>n</i> = 316)	Staphylococci (<i>n</i> = 150)	BHS (<i>n</i> = 24)	ANHS (<i>n</i> = 96)	Enterococci (<i>n</i> = 46)	<i>p</i>
<i>Biological parameters</i>						
Number of positive blood culture bottles†	3.3 ± 2.1	3.9 ± 2.4	1.8 ± 1.6†	3.0 ± 1.6†	2.8 ± 1.6	<0.0001
Number of positive blood culture bottles/number of samples	0.93 ± 0.2	0.96 ± 0.1	0.81 ± 0.4	0.9 ± 0.2	0.93 ± 0.2	0.02
Serum C-reactive protein level (mg/L)†	174 ± 102	210 ± 105	208 ± 130†	110 ± 51†	127 ± 59	<0.0001
Serum BNP level, median (ng/L) [IQR]	511 [799]	421 [902]	518 [1128]	447 [661]	799 [785]	0.33
Serum troponin level, median (µg/L) [IQR]†	0.18 [0.9]	0.22 [1.1]	0.44 [8.3]†	0.07 [0.24]†	0.17 [0.9]	0.01
<i>Echocardiographic parameters</i>						
Maximal length of vegetation (mm)	14.4 ± 7.5	15.4 ± 8.4	13.8 ± 6.3	13.6 ± 6.5	12.7 ± 7.3	0.23
Severe or important valve insufficiency†	128 (40.5%)	47 (31.3%)	7 (29.2%)†	54 (56.3%)†	20 (43.5%)	<0.001
Valvular perforation†	95 (30.0%)	36 (24.0%)	4 (16.7%)†	42 (43.8%)†	13 (28.3%)	<0.01
Periprosthetic regurgitation	18 (5.7%)	6 (15.4%)	1 (25.0%)	5 (16.1%)	6 (28.6%)	0.53
Intracardiac abscess	67 (21.2%)	32 (21.3%)	4 (16.7%)	15 (15.6%)	16 (34.8%)	0.07
<i>Systemic embolism</i>						
Cerebral ischemia (on CT and/or MRI) (<i>n</i> = 230)	104 (45.2%)	51 (45.9%)	11 (61.1%)	26 (37.7%)	16 (50.0%)	0.33

Cerebral hemorrhage (including microbleed) (<i>n</i> = 230)	50 (21.7%)	27 (24.3%)	3 (16.7%)	16 (23.2%)	4 (12.5%)	0.52
Other tomographic non-cerebral embolism (<i>n</i> = 266)	93 (35.0%)	54 (45.8%)	3 (13.6%)	22 (26.2%)	14 (33.3%)	0.04
Spondylodiscitis	31 (9.8%)	12 (8.0%)	1 (4.2%)	11 (11.5%)	7 (15.2%)	0.38

Management

Time to diagnosis (days) [†]	24.7 ± 32.4	15.7 ± 24.2	17.7 ± 27.3 [†]	36.5 ± 37.2 [†]	33.0 ± 37.9	<0.0001
Cardiac surgery	166 (52.5%)	67 (44.7%)	11 (45.8%)	61 (63.5%)	27 (58.7%)	0.02
Time to surgical procedure (days)	15.9 ± 14.6	13.5 ± 10.9	15.4 ± 11.9	18.3 ± 17.8	16.5 ± 15.7	0.32
Duration of antibiotic therapy (days)	53.2 ± 19.5	57.5 ± 21.1	43.3 ± 7.3	49.4 ± 19.8	54.5 ± 15.9	<0.01
Treatment including aminoglycosides	229 (72.5%)	100 (66.7%)	19 (79.2%)	77 (80.2%)	33 (71.7%)	0.11
Duration of aminoglycoside therapy (days)	6.0 ± 4.6	5.2 ± 3.2	5.5 ± 6.9	6.5 ± 5.1	6.8 ± 4.9	0.26
Length of in-hospital stay (days)	38.0 ± 21.4	40.8 ± 24.5	34.8 ± 16.1	36.2 ± 19.3	35.5 ± 18.0	0.33

Values are presented as n (%) or the mean ± standard deviation, as appropriate, unless otherwise specified.

[†] *p* < 0.05 for the comparison between BHS and ANHS

Abbreviations: IE, infective endocarditis; BHS, beta-hemolytic streptococci; ANHS, alpha- or non-hemolytic streptococci; BNP, brain natriuretic peptide; CT, computed tomography; MRI, magnetic resonance imaging; IQR, interquartile range

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Table 3 Complications and outcomes of 316 patients with IE according to the causative microorganism

	Total	Staphylococci	<i>S. aureus</i>	BHS	ANHS	Enterococci	<i>P</i> [#]	<i>p</i> [*]	OR
	(<i>n</i> = 316)	(<i>n</i> = 150)	(<i>n</i> = 115)	(<i>n</i> = 24)	(<i>n</i> = 96)	(<i>n</i> = 46)			(95% CI)*
In-hospital mortality	60 (19.0%)	40 (26.7%)	34 (29.6%)	6 (25.0%)	9 (9.4%)	5 (10.9%)	<0.001	0.08	3.18 (0.82–11.56)
One-year mortality	67 (21.2%)	44 (29.3%)	37 (32.2%)	6 (25.0%)	10 (10.4%)	7 (15.2%)	<0.001	0.09	2.84 (0.75–10.00)
Septic shock†	57 (18.0%)	44 (29.3%)	41 (35.7%)	7 (29.2%)	3 (3.1%)	3 (6.5%)	<0.0001	<0.001	12.35 (2.52–81.33)
Heart failure	169 (53.5%)	79 (52.7%)	63 (54.8%)	16 (66.7%)	51 (53.1%)	23 (50.0%)	0.60	0.23	1.76 (0.64–5.22)
Clinically significant stroke	49 (15.5%)	27 (18.0%)	22 (19.1%)	7 (29.2%)	12 (12.5%)	3 (6.5%)	0.04	0.06	2.85 (0.83–9.31)

Values are presented as n (%).

[#]Data regarding comparisons between *S. aureus*, BHS, ANHS and Enterococci.

^{*}Data regarding comparisons between BHS and ANHS.

Abbreviations: IE, infective endocarditis; BHS, beta-hemolytic streptococci; ANHS, alpha- or non-hemolytic streptococci; OR, odds ratio; CI, confidence interval