

# HACEK endocarditis

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# Conflict of interest

- None

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# Menu

## ■ Microbiology

- HACEK group
- Taxonomic changes

## ■ Diagnosis

- Prolonged incubation ?
- Identification / Drug susceptibility testing (DST)

## ■ Clinical features

- HACEK bacteremia ↔ endocarditis
- HACEK endocarditis vs. other infective endocarditis (IE)
- H, A, C, E, K endocarditis



# The HACEK group

- **Gram-negative bacteria**

- Pleomorphic, bacilli or coccobacilli

- **Fastidious**

- CO<sub>2</sub> / Enriched media (*as in current automated blood cultures systems*)

- **Part of the human microbiota**

- oropharyngeal
- Urogenital, lower digestive tract

- **Specific tropism for cardiac valves**

- Although Gram negative
- **For some, the only disease they know !**

# HACEK, taxonomic changes

- ***Haemophilus para-influenzae***

- ***Aggregatibacter* spp.**

- A. actinomycetemcomitans*
- A. aphropilus*
- A. paraphropilus*
- A. segnis*

- ***Cardiobacterium* spp.**

- C. hominis*
- C. valvarum*

- ***Eikenella corrodens***

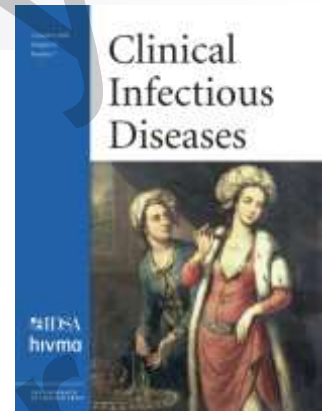
- ***Kingella* spp.**

- K. kingae*
- K. denitrificans*

**Do HACEK require prolonged incubation of blood cultures ?**

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## Prolonged Incubation and Extensive Subculturing Do Not Increase Recovery of Clinically Significant Microorganisms from Standard Automated Blood Cultures



### ■ Observational study (Sandford Univ)

- 1995-1997: extensive BC protocol, including prolonged incubation (3 weeks), for **all patients with suspected IE but negative BC**
- **215 patients** enrolled => **no HACEK** identified after 5 days
- **24 HACEK bacteremia** were documented with positive BC before day 5

# Utility of Extended Blood Culture Incubation for Isolation of *Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella* Organisms: a Retrospective Multicenter Evaluation

## ■ Multicenter observational retrospective US study

- Automated BC systems (BacT/Alert or BACTEC)
- HACEK represented < 1% of positive BC (35 / 59,203)
- **Mean/median time to HACEK detection = 2-3 days**
- **Prolonged incubation (> 5 days) performed for 407 BC bottles => no HACEK**

Study site(s)	Total no. of positive blood cultures	HACEK bacteria isolated (no. of cultures)	Time to detection in days (no. of cultures)
ARUP	2,301	<i>Haemophilus parainfluenzae</i> (1)	4
DUMC	48,921 <sup>a</sup>	<i>Eikenella corrodens</i> (3)	1, 3 (2)
		<i>Kingella kingae</i> (1)	2
		<i>Haemophilus</i> spp. (5)	2 (5)
		<i>Haemophilus aphrophilus</i> (1)	2
		<i>Haemophilus haemolyticus</i> (1)	3
		<i>Haemophilus parainfluenzae</i> (15)	2 (7), 3 (6), 7 (2)
JHH	6,519	<i>Actinobacillus actinomycetemcomitans</i> (1)	5
		<i>Eikenella corrodens</i> (1)	4
		<i>Cardiobacterium hominis</i> (2)	3 (2)
		<i>Haemophilus parainfluenzae</i> (3)	3, 4, 5
RWJ	1,462 <sup>b</sup>	<i>Haemophilus parainfluenzae</i> (1)	4
All	59,203	All (35)	3 <sup>c</sup>



# Identification / DST

## ■ Identification through MALDI-TOF reliable and fast

- 66-93% accuracy at species level
- 88-95% at genus level

*Van Veen SQ et al. J Clin Microbiol 2010*

*Couturier MR et al. J Clin Microbiol 2011*

*Powell EA et al. J Clin Microbiol 2013*

*Branda JA et al. Diagn Microbiol Infect Dis 2014*

## ■ DST to be performed by broth microdilution (CLSI 2010)

- How reliable ?
- Some experts raised doubt on validity of DST => 3rd generation cephalosporin for any HACEK IE, whatever DST results

*Coburn B et al. Antimicrob Agents Chemother 2013*

*Baddour LM et al. Circulation 2015*

# Antimicrobial Susceptibilities of Clinical Isolates of HACEK Organisms



- Toronto reference lab for DST
- 174 HACEK isolates (2010-12) => For 104 (60%), DST not reliable

TABLE 1 MICs of antimicrobial agents against clinical HACEK isolates in this study<sup>a</sup>

Drug(s)	All isolates (n = 70)		<i>A. actinomycetemcomitans</i> (n = 2)		<i>A. aphrophilus</i> (n = 11)		<i>H. parainfluenzae</i> (n = 37)		<i>C. hominis</i> (n = 2)		<i>E. corrodens</i> (n = 17)		<i>K. kingae</i> (n = 1)
	MIC range, µg/ml (% S)	MIC <sub>50/90</sub> <sup>b</sup> µg/ml	MIC range, µg/ml (% S)	MIC <sub>50/90</sub> <sup>b</sup> µg/ml	MIC range, µg/ml (% S)	MIC <sub>50/90</sub> <sup>b</sup> µg/ml	MIC range, µg/ml (% S)	MIC <sub>50/90</sub> <sup>b</sup> µg/ml	MIC range, µg/ml (% S)	MIC <sub>50/90</sub> <sup>b</sup> µg/ml	MIC range, µg/ml (% S)	MIC <sub>50/90</sub> <sup>b</sup> µg/ml	MIC, µg/ml
<b>Penicillins</b>													
Amoxicillin-clavulanic acid	≤2 (100)	2	≤2 (100)	ND <sup>d</sup>	≤2 (100)	2	≤2 (100)	2	≤2 (100)	ND	≤2 (100)	2	S ≤2
Ampicillin-sulbactam	≤1-2 (97.1)	1/1	≤1->2 (50)	ND	≤1 (100)	1/1	≤1->2 (97.3)	1/2	≤1 (100)	ND	≤1 (100)	1/1	S ≤1
Ampicillin	≤0.12->4 (95.8)	0.25/1	0.5-4 (50)	ND	≤0.12-1 (100)	0.5/0.5	≤0.12->4 (97.3)	0.25/1	≤0.12-0.25 (100)	ND	≤0.12->4 (94.1)	0.25/1	S ≤0.12
Penicillin	≤0.015->1 (77.1)	0.5/>1	1->1 (50)	ND	≤0.015->1 (81.8)	0.5/>1	≤0.015->1 (67.6)	1/>1	0.06-0.12 (100)	ND	0.12->1 (94.1)	0.5/1	S 0.03
<b>Cephalosporins</b>													
Ceftriaxone	≤0.03-0.5 (100)	0.03/0.12	≤0.03-0.25 (100)	ND	≤0.03 (100)	0.03/0.03	≤0.03-0.5 (100)	0.03/0.03	0.06-0.25 (100)	ND	≤0.03-0.5 (100)	0.03/0.12	S ≤0.03
Cefixime	≤0.12->1	0.12/0.25	≤0.12-0.25	ND	≤0.12-0.25	0.12/0.12	≤0.12-0.5	0.12/0.12	≤0.12->1	ND	≤0.12->1	0.12/>1	- ≤0.12
Cefepime	≤0.12->2	0.12/0.5	0.25->2	ND	≤0.12-0.25	0.12/0.12	≤0.12->2	0.12/0.5	≤0.12-0.5	ND	≤0.12-2	0.12/0.5	- ≤0.12
Cefuroxime	≤0.5-8	0.5/2	≤0.5-2	ND	≤0.5	0.5/0.5	≤0.5-1	0.5/1	≤0.5	ND	≤0.5-8	2/8	- ≤0.5
Cefaclor <sup>b</sup>	≤4->16 <sup>b</sup>	4/4 <sup>b</sup>	≤4	ND	≤4	4/4	≤4->16	4/4	≤4	ND	≤4-8 <sup>b</sup>	4/8 <sup>b</sup>	- ≤4
<b>Carbapenems</b>													
Meropenem	≤0.06-0.25 (100)	0.06/0.06	≤0.06-0.25 (100)	ND	≤0.06 (100)	0.06/0.06	≤0.06 (100)	0.06/0.06	≤0.06 (100)	ND	≤0.06 (100)	0.06/0.06	S ≤0.06
Imipenem	≤0.5-1 (ND) <sup>c</sup>	0.5/0.5	≤0.5-1 (100)	ND	≤0.5 (100)	0.5/0.5	≤0.5-1 (97.3)	0.5/0.5	≤0.5 (100)	ND	≤0.5 (100)	0.5/0.5	S ≤0.5
<b>Fluoroquinolones</b>													
Levofloxacin	≤0.03-0.25 (100)	0.03/0.12	≤0.03 (100)	ND	≤0.03-0.06 (100)	0.03/0.06	≤0.03-0.25 (100)	0.03/0.12	≤0.03-0.25 (100)	ND	≤0.03-0.25 (100)	0.03/0.06	S ≤0.03
Sparfloxacin	≤0.03-1	0.03/0.12	≤0.03	ND	≤0.03-0.25	0.03/0.06	<0.03-1	0.03/0.12	≤0.03	ND	≤0.03-0.12	0.03/0.06	- ≤0.03
<b>Other agents</b>													
Chloramphenicol	≤0.5-2 (100)	1/2	≤0.5-1 (100)	ND	≤0.5-2 (100)	0.5/1	≤0.5-2 (100)	0.5/2	≤0.5-1 (100)	ND	1-2 (100)	1/2	S ≤0.5
Tetracycline	≤0.25-2 (98.6)	1/1	0.5-1 (100)	ND	≤0.25-2 (100)	0.25/2	≤0.25->4 (97.3)	0.25/2	≤0.25-5	ND	0.5-1 (100)	0.5/1	S ≤0.25
Sulfamethoxazole-trimethoprim <sup>b</sup>	≤0.06->2 (93.2) <sup>b</sup>	0.06/0.25 <sup>b</sup>	≤0.06 (100)	ND	≤0.06-0.25 (100) <sup>b</sup>	0.06/0.25 <sup>b</sup>	≤0.06->2 (86.2) <sup>b</sup>	0.06/1 <sup>b</sup>	≤0.06-0.25 (100)	ND	≤0.06-0.5 (100) <sup>b</sup>	0.06/0.5	S ≤0.06
Clarithromycin	≤0.12-16 (55.7)	4/16	8-16 (50)	ND	≤0.12->16 (54.5)	0.12/>16	0.25->16 (32.4)	16/>16	≤0.12-8 (100)	ND	2-8 (100)	2/8	S 0.25
Erythromycin	≤0.25->0.5	>0.5/>0.5	>0.5	ND	>0.5	>0.5							

**Do all HACEK have similar tropism for cardiac valves ?**

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# Association between HACEK bacteraemia and endocarditis



## ■ Retrospective multicenter study

- 87 cases of HACEK bacteremia (1979-2011)

Micro-organism	No. cases (%)	Total no. endocarditis cases (definite/possible) by Duke criteria	PPV (%)
<i>H. parainfluenzae</i>	18 (20.7)	10 (7/3)	55
<i>A. actinomycetemcomitans</i>	18 (20.7)	18 (9/9)	100
<i>A. aphrophilus</i>	9 (10.3)	5 (3/2)	55
<i>A. paraphrophilus</i>	4 (4.6)	4 (4/0)	100
<i>Cardiobacterium</i> spp.	8 (9.2)	7 (5/2)	88
<i>E. corrodens</i>	11 (12.6)	0	0
<i>Kingella</i> spp.	19 (21.8)	8 (7/1)	42
Total	87 (100)	52 (35/17)	60

# Characteristics of HACEK endocarditis

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# HACEK Infective Endocarditis: Characteristics and Outcomes from a Large, Multi-National Cohort



HACEK organisms	Number (%)
<b><i>Haemophilus spp.</i></b>	<b>31 (40)</b>
<i>Haemophilus parainfluenzae</i>	28 (36)
<i>Haemophilus sp. other</i> <sup>a</sup>	3 (4)
<b><i>Aggregatibacter spp.</i></b>	<b>26 (34)</b>
<i>Aggregatibacter actinomycetemcomitans</i>	15 (20)
<i>Aggregatibacter aphrophilus</i>	5 (6)
<i>Aggregatibacter paraphrophilus</i>	5 (6)
<i>Aggregatibacter segnis</i>	1 (1)
<b><i>Cardiobacterium spp.</i></b>	<b>11 (14)</b>
<i>Cardiobacterium hominis</i>	10 (13)
<i>Cardiobacterium valvarum</i>	1 (1)
<b><i>Eikenella corrodens</i></b>	<b>4 (5)</b>
<b><i>Kingella spp.</i></b>	<b>4 (5)</b>
<i>Kingella kingii.</i>	2 (3)
<i>Kingella denitrificans</i>	1 (1)
<i>Kingella sp.</i>	1 (1)
<b>HACEK (not otherwise specified)</b>	<b>1 (1)</b>
<b>Total</b>	<b>77</b>

- **Prospective cohort study**

- 2000-2006
- 64 sites, 28 countries

- **77 HACEK IE (1.4% of all IE)**

# HACEK Infective Endocarditis: Characteristics and Outcomes from a Large, Multi-National Cohort



	HACEK endocarditis (n = 77)	Non-HACEK IE (n = 5 514)	P
Age, years (median, IQR)	47.4 (35.6–57.1)	60.5 (45.3–72.7)	< 0.001
Immunologic events, n (%)	25 (32%)	1 118 (20%)	0.008
Stroke, n (%)	19 (25%)	898 (17%)	0.05
Heart failure, n (%)	11 (15%)	1 646 (30%)	0.004
<b>In-hospital mortality, n (%)</b>	<b>3 (4%)</b>	<b>998 (18%)</b>	<b>0.001</b>

# INFECTIVE ENDOCARDITIS CAUSED BY HACEK MICROORGANISMS

## ■ Retrospective study

- 1970-1992 => 45 HACEK endocarditis

**Table 2** Duration of symptoms prior to diagnosis

Species <sup>a</sup>	<2 weeks	2 wk–3 mo	3–6 mo	>6 mo
H	5	10	2	2
A	0	5	3	1
C	0	2	6	4
E	0	1	1	0
K	1	2	0	0

<sup>a</sup>H, *Hemophilus*; A, *Actinobacter*; C, *Cardiobacterium*; E, *Eichenella*; K, *Kingella*.

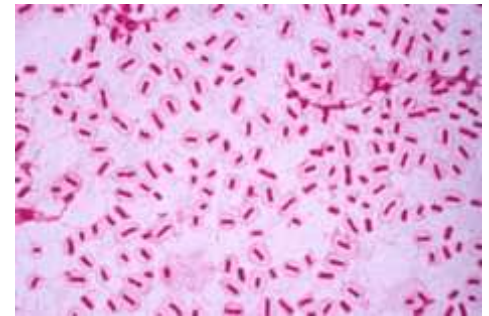


## Retrospective study, Rennes Univ. Hosp.

- 1993-2016 => 18 HACEK endocarditis (**2% of all IE**)
- **Mean age, 56 years**
- **Mean duration of symptoms before diagnosis, 36 days**
- **Stroke, n=9 (50%)**
- **Cardiac surgery, n=10**
- **Survival, 100% (one relapse)**

# *Haemophilus para-influenzae* endocarditis

- Most common cause of HACEK IE, with *Aggregatibacter* sp.
- **Mean age, 47 years**
- **Mean duration of symptoms before diagnosis, 36 days**
- **Stroke, 21%**
- **Cardiac surgery, 42%**
- **Survival, 95%**



Pleomorphic Gram negative coccobacilli

# Aggregatibacter endocarditis

- Most common cause of HACEK IE, with *Haemophilus para-influenzae*
- *A. actinomycetemcomitans* => aggressive periodontitis
- **Mean age, 47 years**
- **Mean duration of symptoms before diagnosis, 100 days !**
- 42% associated with dental disease
- Stroke, 30%
- Cardiac surgery, 25%
- Survival, 82%



Pleomorphic Gram negative coccobacilli

# Cardiobacterium endocarditis

- 3rd cause of HACEK IE, after *H. para-influenzae*, and *Aggregatibacter*
- **Mean age, 50 years**
- **Mean duration of symptoms before diagnosis, 138-169 days !**
- Stroke, 21%
- Cardiac surgery, 45%
- Survival, 93%



Teardrop forms, Gram negative bacilli

*Wormser GP et al. Rev Infect Dis 1983*

*Malani AN et al. Eur J Clin Microbiol Infect Dis 2006*

## ***Eikenella corrodens* endocarditis**

- Rare cause of HACEK IE (5%), limited tropism for cardiac valves
- **Normal microbiota of humans (oral cavity, saliva)**
  - Bites
  - IVDU

## ***Kingella sp.* endocarditis**

- Rare cause of HACEK IE (5%), **except in children (40-50%)**
- **Most common cause of arthritis in children <4 year-old**

# Association between HACEK bacteraemia and endocarditis



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Total	87 (100)	52 (35/17)	60

# Treatment of HACEK IE

## ■ Not evidence-based

- No clinical trial
- Heterogeneous, observational studies, small sample size
- Prognosis good anyway (>95% cure)

## ■ Words of caution

- DST may not be reliable, even in experts hands (fastidious bacteria)
- Resistance have been reported, beta-lactamase may be emerging

⇒ 3rd generation cephalosporin first choice, no combination

⇒ Alternative (allergy) = cipro or levofloxacin

# HACEK IE: Take-home messages

- **Diagnosis does not require prolonged incubation of BC**
- **All HACEK were not created equal (H, A, and C much more associated with IE)**
- **Characteristics of HACEK IE (vs. other IE)**
  - **Insidious => late diagnosis** (1-6 months after symptoms onset)
  - Younger patients, more stroke, less heart failure
- **Treatment**
  - Criteria for cardiac surgery = as for any IE
  - **Medical treatment = 3rd generation cephalosporin, whatever DST**
  - **No patient is allowed to die !**