Epidemiological, retrospective, multicenter study on the clinical-epidemiological characteristics and therapeutic management of non-cholera Vibrio infections.

INFECTIVE

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Sponsor

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HISTORY OF PROTOCOL UPDATES

VERSION	DATE	RAISON DE LA MISE A JOUR
1	09/12/2019	
2	23/01/2020	Amendments in accordance with the recommendations of the Comité d'expertise pour les recherches, les études et les évaluations dans le domaine de la santé
2.1	23/01/2020	English version

SOMMAIRE

1. SUMMARY

SPONSOR	Groupe Hospitalier La Rochelle Ré Aunis Rue du Dr Schweitzer - 17019 La Rochelle
STUDY DIRECTOR	Dr Florence Hoefler
TITLE	Epidemiological, retrospective, multicenter study on the clinical-epidemiological characteristics and therapeutic management of non-cholera Vibrio infections (INFECTIVE).
CONTEXT	Vibrios are gram-negative, ubiquitous bacteria of the marine flora and are found particularly in warm waters. For example, the incidence is high in Florida and Vibrio infections are now reportable in the United States. Different species of Vibrio are described. We distinguish between choleric vibrios belonging to serogroups O1 and O139, responsible for cholera epidemics, and non-choleric vibrios. Our study will focus on non-epidemic vibrios. Vibrio infections develop by eating contaminated raw seafood or by exposure of a wound to the marine environment. They occur mainly during the hot summer months. This is explained on the one hand by a higher water temperature and on the other hand by an increased use of the beaches. With global warming, it is possible that Vibrio infections may increase in number and location.
OBJECTIVES	The purpose of this study is to identify the epidemiological and clinical characteristics of patients diagnosed with non-cholera Vibrio infection in Western France from 2000 to 2019. The different clinical forms will be described according to the different environmental and meteorological contexts.
DESIGN	Data-driven, retrospective, multi-center study
INCLUSION CRITERIA	- cases of non-epidemic vibriosis
EXCLUSION CRITERIA	- cases of infection with Vibrio cholerae O1 and O139
OUTCOME MEASURES	Socio-demographic, clinical and therapeutic criteria.
SAMPLE SIZE	Estimation entre 50 et 60 patients
STATISTICAL ANALYSIS	The data will be analyzed in a descriptive manner, and will be described by mean, standard deviation and median for continuous variables and by percentages for categorical variables.

2. SCIENTIFIC JUSTIFICATION AND GENERAL DESCRIPTION

2.1. CURRENT STATE OF KNOWLEDGE

Vibrios are gram-negative, ubiquitous bacteria of the marine flora and are found particularly in warm waters. For example, the incidence is high in Florida and Vibrio infections are now reportable in the United States. [1].
Different species of Vibrio are described. We distinguish between choleric vibrios belonging to serogroups O1 and O139, responsible for cholera epidemics, and non-choleric vibrios. Our study will focus on non-epidemic vibrios. Among the non-epidemic vibrios, the predominant species are *Vibrio vulnificus*, *Vibrio parahaemolyticus*, *Vibrio algolyticus* and non-O1/O139 *Vibrio cholerae*.
Vibrio infections develop by eating contaminated raw seafood - especially oysters - or by exposure of a wound to the marine environment. [2]. They occur mainly during the hot summer months. This can be explained on the one hand by a higher water temperature and on the other hand by an increased use of the beaches [3]. With global warming, it is possible that Vibrio infections may increase in number and location.

Vibrio infections are rare but can be very severe or even fatal. They present themselves in the form of gastroenteritis, severe dermohypodermatitis or necrotizing fasciitis and can lead to septic shock.
They are more common in patients with multiple co-morbidities including liver disease and heart failure [4].

Due to their rarity, Vibrio infections are very little known and therefore probably under-diagnosed. A delay in the therapeutic management with, in particular, targeted antibiotic therapy has been highlighted. [1]. Given the potential seriousness of these infections, it is important to sensitize healthcare professionals to take Vibrio into account in their therapeutic strategy when risk factors are identified (exposure to the marine environment, consumption of seafood).

2.2. JUSTIFICATION OF THE REQUEST FOR DEROGATION FROM INDIVIDUAL INFORMATION

The rarity of cases requires data collection from old records. It is planned to go back as far as 2000. A significant number of patients, who will no longer be followed up in the center where the diagnosis of vibriosis was made, is therefore to be expected. An authorization for a waiver of information is being sought as it will be difficult to locate the patients concerned.

3. OBJECTIVES

3.1. PRIMARY OBJECTIVE

To describe the clinical and epidemiologic characteristics of patients diagnosed with non-cholera Vibrio infection.

3.2. SECONDARY OBJECTIVES

Describe the different clinical forms (gastroenteritis, moderate to severe skin disorders, bacteremia, ear infections) according to the different environmental contexts, particularly meteorological.

4. DESIGN

Data-driven, retrospective, multi-center study

5. ELIGIBILITY CRITERIA

5.1. INCLUSION CRITERIA

Cases of vibriosis, other than Vibrio cholerae O1-O139, diagnosed between January 2000 and November 2019 will be included.

A non-epidemic Vibrio infection is defined by a biological sample (blood culture, superficial sample, deep sample, ear sample) positive to a Vibrio species other than Vibrio cholerae O1-O139 taken from any patient.

5.2. EXCLUSION CRITERIA

Cases of Vibrio cholerae O1 and O139.

5.3. FEASIBILITY AND RECRUITEMENT METHODS

The data are collected in the hospital centers participating in the study, using a data collection form, directly by the person in charge of the study (Dr Florence Hoefler).

The participating centers are the hospital centers of Poitiers, La Rochelle, Tours, La Roche-sur-Yon, Nantes, Angers and Rennes.

A information letter will be sent to patients for whom the address is available.

Identity	Specialty	Institution	Professional registration number	Centre N°
Dr HOEFLER Florence	Maladies infectieuses	GH de la Rochelle Ré Aunis	10101395555	01
Pr France ROBLOT	Maladies infectieuses et tropicales	CHU de Poitiers	10002717147	02
Pr Louis BERNARD	Médecine interne	CHU de Tours	10001058394	03
Dr Thomas GUIMARD	Unité d'Infectiologie	CH Départemental de la Vendée	10100112449	04
Pr David BOUTOILLE	Maladies infectieuses et tropicales	CHU de Nantes	10002582244	05
Dr Pierre ABGUEGUEN	Maladies infectieuses	CHU d'Angers	10002575198	06
Pr Pierre TATTEVIN	Service de Maladies Infectieuses et Réanimation Médicale	CHU de Rennes	10002669595	07
Pr Didier NEAU	Maladies infectieuses et tropicales	CHU de Bordeaux	10002772936	08

Non-epidemic Vibrio infections are rare, and extending the research to eight centers over 20 years allows us to collect as many cases as possible. Data extraction will be done via the computer software in the microbiology laboratory of each center. Extraction may not be feasible until the year 2000 depending on the different centers, which will be indicated within the limits of the study. The clinical records will then be consulted on the computer system of each center.

6. EVALUATION CRITERIA

6.1. PRIMARY OUTCOME

Socio-demographic, clinical and therapeutic criteria.

Details about the variables collected:

Non-epidemic Vibrio infections can give four main clinical pictures:
1) skin infections ranging from simple dermohypodermatitis to necrotizing fasciitis (skin damage with sores, blisters or necrosis will be sought)
2) Digestive infections such as acute gastroenteritis (diarrhea, nausea, vomiting).
3) bacteremia with a more or less severe sepsis pattern (fever, hemodynamic instability, dyspnea). The entry portal can be varied: digestive, cutaneous or pulmonary.
4) ENT infections such as chronic otitis media (we will look for ear pain, discharge, deafness).

Finally, Vibrio infections also give other clinical pictures but less common: pneumonia from inhaling contaminated water (typically from drowning), bone infections from an open fracture in contact with contaminated water.

Vibrio infections are more common when the water temperature rises. More infections are expected during the summer months (June to September). It is therefore interesting to collect the month of exposure and infection in order to confirm this hypothesis.

Therapeutic management is essentially based on antibiotic therapy. The literature shows that the initial antibiotic therapy is often not adapted because Vibrio is rarely taken into account in the first diagnoses. It is therefore voluntary to let the antibiotic therapy be specified rather than restricting the choice to a few molecules. Finally, in severe skin infections such as necrotizing fasciitis, surgical treatment such as debridement, lavage or amputation is necessary. Sometimes there is a need for several surgical revisions.

7. STATISTICAL ANALYSIS

Statistical analyses will be carried out by :
Caroline Allix-Béguec, PhD
Unité de recherche clinique
Groupe Hospitalier de la Rochelle Ré Aunis
17019 La Rochelle Cedex
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7.1. SAMPLE SIZE

The study carried out by the National Reference Center for Vibriosis and Cholera between January 1995 and December 1998 reported 29 cases of non-cholera vibriosis infections [5]. More than half (n=16) resided in a coastal department and 7 were from the Atlantic coast.

Vibrios do not develop in waters with a high degree of salinity, which is why they are rarely isolated in France.
Data collection in the hospital centers of Poitiers, La Rochelle, Tours, La Roche-sur-Yon, Nantes, Angers, Rennes and Bordeaux will make it possible to describe almost all Bay of Biscay and Celtic sea cases. Between 50 and 60 cases are thus expected over a period of 19 years in all participating centers.

7.2. STATISTICAL ANALYSIS

Between 50 and 60 cases are thus expected over a period of 19 years in all participating centers.

8. RIGHTS OF ACCESS TO SOURCE DATA AND DOCUMENTS

8.1. ACCES TO DATA

Acceptance of participation in the protocol implies that the persons carrying out the research will make the documents and individual data strictly necessary for the monitoring, quality control and auditing of the research available to persons with access to these documents in accordance with the legislative and regulatory provisions in force.

8.2. SOURCE DATA

All information contained in original documents, or in authenticated copies of such documents, relating to clinical examinations, observations or other activities carried out in the course of research and necessary for the reconstruction and evaluation of the research. Documents in which source data are recorded are referred to as source documents.
Source documents are patient medical records.

8.3. CONFIDENTIALITY

In accordance with the legislative provisions in force, persons with direct access to source data shall take all necessary precautions to ensure the confidentiality of information relating to the research, the persons involved, particularly with regard to their identity and the results obtained. These persons, in the same way as the persons directing and supervising the research, are subject to professional secrecy.

During or at the conclusion of the research, data collected on individuals who are suitable for the research and provided to the sponsor by those conducting and monitoring the research (or other specialized stakeholders) will be coded. Under no circumstances should the names or addresses of the individuals concerned be made clear.

The coding used will be as follows:

ID : |_| |_| |_| |_| |_|

1st letter of patient surname	1st letter of patient first name	No centre	No patient

9. QUALITY CONTROL AND QUALITY ASSURANCE

9.1. INSTRUCTIONS FOR DATA COLLECTION

All information required by the protocol should be recorded on the paper case report forms and an explanation should be provided for each missing data item. Data should be collected as they are obtained, and recorded in these notebooks in a neat and legible manner.

9.2. RESEARCH FOLLOW-UP

Dr. Hoefler will follow up on the research. She will be in charge of :

- the logistics and monitoring of the research,
- reporting on its progress,
- the verification of the update of the observation book (request for additional information, corrections, ...),

She will work according to standard operating procedures.

9.3. DATA MANAGEMENT

The data will be entered on an Excel database stored on the developer's internal network protected from intrusions and with a daily backup system on disk.
Consistency tests (data format, search for extremes) will be performed by the statistician who will provide feedback to Dr. Hoefler for verification of the data.
The database will be frozen after the responses to all queries are received.

9.4. AUDIT AND INSPECTION

An audit may be carried out at any time by persons mandated by the sponsor and independent of the persons conducting the research. Its purpose is to verify the safety of participants and respect for their rights, compliance with applicable regulations and the reliability of data.
The audit, as well as the inspection, may apply to all stages of the research, from the development of the protocol to the publication of the results and the classification of the data used or produced in the course of the research.

Investigators agree to comply with the sponsor's requirements for an audit and with the competent authority for an inspection of the research.

10. ETHICAL AND REGULATORY CONSIDERATIONS

10.1. COMPLIANCE WITH REFERENCE TEXTS

The data recorded during this research is subject to computerized processing at the Groupe Hospitalier de la Rochelle Ré Aunis in compliance with law n°78-17 of January 6, 1978 relating to data processing, files and liberties modified by law 2004-801 of August 6, 2004.

The Groupe Hospitalier de la Rochelle Ré Aunis has declared the research to the Commission Nationale de l'Informatique et des Libertés (CNIL).

11. ARCHIVE OF DOCUMENTS AND RESEARCH DATA

The conservation of data from this study will be carried out in accordance with the institution's procedure for the conservation and archiving of research documents.
The references of this procedure are the decree of August 11, 2008 modifying the decree of November 8, 2006 setting the duration of storage by the sponsor and the investigator of documents and data relating to biomedical research involving medicinal products for human use and the decree of August 11, 2008 setting the duration of storage by the sponsor and the investigator of documents and data relating to biomedical research other than that involving medicinal products for human use.
The documents and data relating to the research constitute the essential documents that make up the permanent record of the research. These documents, individually and collectively, enable the evaluation of the conduct of biomedical research and the quality of the data produced. These documents serve to demonstrate that the investigator, the sponsor, and all those involved in the research comply with the laws and regulations in force.

The following documents will be archived in the service until the end of the useful life. This indexed archiving includes:

- Mail copies of the favorable opinion of the Committee of Expertise for Research, Studies and Evaluations in the field of Health (CEREES) and the authorization of the CNIL (French National Commission for Information Technology and Civil Liberties).
- Successive versions of the protocol (identified by version number and version date),
- The completed and validated observation notebook of each subject included,
- All the specific appendices of the study,
- The final study report from the statistical analysis and quality control of the study (duplicate sent to the sponsor).
- Any audit certificates carried out during the course of the research

The database having given rise to the statistical analysis must also be archived by the person in charge of the analysis.

At the end of the period of practical usefulness, all documents to be archived, as defined in the procedure of "filing and archiving of documents related to biomedical research" of the Groupe Hospitalier de la Rochelle Ré Aunis will be transferred to the archiving site dedicated to clinical research and will be placed under the responsibility of the Sponsor for 15 years after the end of the study in accordance with institutional practices.

12. RULES RELATING TO PUBLICATION

12.1. SCIENTIFIC COMMUNICATIONS

The analysis of the data provided by the centers is carried out by the Groupe Hospitalier de la Rochelle Ré Aunis. This analysis results in a written report that is submitted to the sponsor. This report allows the preparation of one or more publications.

Any written or oral communication of the results of the research must receive the prior agreement of the person conducting and supervising the research and, where applicable, of any committee established for the research.

The publication of the main results mentions the name of the sponsor, all persons who included or followed up patients in the research, and the methodologists, biostatisticians and data managers who participated in the research. The international rules for writing and publication will be taken into account (The Uniform Requirements for Manuscripts of the ICMJE, April 2010).

12.2. COMMUNICATION OF RESULTS TO PATIENTS

At their request, research participants are informed of the overall results of the research.

12.3. TRANSFER OF DATA

Data collection and management is provided by the Groupe Hospitalier de la Rochelle Ré Aunis. The conditions of transfer of all or part of the research database are decided by the research sponsor and are the subject of a written contract.

13. REFERENCES

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[3] Givens CE, Bowers JC, Depaola A, Hollibaugh JT, Jones JL. Occurrence and distribution of Vibrio vulnificus and Vibrio parahaemolyticus - potential roles for fish, oyster, sediment and water. Lett Appl Microbiol 2014;58:503–510. doi:10.1111/lam.12226.

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[5] Geneste C, Dab W, Cabanes P, Vaillant V, Quilici M, Fournier J. Les vibrioses non cholériques en France : cas identifiés de 1995 à 1998 par le Centre National de Référence. Bull Epidémiologique Hebd 2000;9:38–40.