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The microbiological epidemiology of infections in peritoneal dialysis over a 45-year period in the Peritoneal Dialysis Registry in France (RDPLF)

(Épidémiologie microbiologique des infections en dialyse péritonéale sur une période de 45 ans, d'après le registre de dialyse péritonéale en France (RDPLF))

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Summary

Infectious peritonitis remains a frequent complication of peritoneal dialysis. Over the years, numerous technical advancements have been introduced, aimed at both reducing the incidence of these infections and enhancing their microbiological characterization. In this study, we analyzed 26,235 peritonitis episodes recorded in the French-Language Peritoneal Dialysis Registry (RDPLF) database to describe the evolution of infectious epidemiology from the 1980s to the present day.

Our findings reveal a marked decrease in the proportion of staphylococcal infections between 1978 and 2010. Conversely, infections caused by Enterobacteriaceae, enterococci, and streptococci have progressively increased over the same period. The modality of peritoneal dialysis appears to be associated with specific bacterial profiles: infections involving skin flora are more prevalent in continuous ambulatory peritoneal dialysis, whereas those of environmental or mixed (oral/gastrointestinal) origin are more frequently observed with automated peritoneal dialysis.

The advent of advanced diagnostic techniques, particularly molecular biology methods, has significantly improved the microbiological documentation of peritonitis, especially for organisms that are non-cultivable or difficult to culture by conventional laboratory methods.

In summary, this study presents the microbiological trends observed in peritoneal dialysis-associated peritonitis in France from the 1980s to the present, based on data from over 20,000 patients included in the RDPLF database, and highlights the impact of evolving technological approaches on the detection and understanding of these infections.

Keywords: peritoneal dialysis, infection, peritonitis,microbiology

Résumé

Les péritonites infectieuses constituent une complication fréquente de la dialyse péritonéale. Au fil des décennies, de nombreuses améliorations techniques ont été mises en œuvre, tant pour réduire l'incidence de ces infections que pour en optimiser la documentation microbiologique. Dans ce contexte, nous avons analysé 26 235 épisodes de péritonites recensés dans la base de données du Registre de Dialyse Péritonéale de Langue Française (RDPLF), dans le but de décrire l'évolution de l'épidémiologie infectieuse depuis les années 1980 jusqu'à nos jours.

Les résultats mettent en évidence une diminution significative de la proportion d'infections à staphylocoques entre 1978 et 2010. En parallèle, une augmentation progressive des infections à entérobactéries, entérocoques et streptocoques a été observée sur la même période. Par ailleurs, le type de modalité de dialyse péritonéale semble associé à des profils microbiologiques distincts : les péritonites dues à des germes issus de la flore cutanée sont plus fréquemment observées en dialyse péritonéale continue ambulatoire (DPCA), tandis que les infections d'origine environnementale ou mixte (orale/digestive) prédominent en dialyse péritonéale automatisée (DPA).

L'émergence de techniques diagnostiques innovantes, notamment la biologie moléculaire, a par ailleurs permis d'améliorer significativement la documentation microbiologique de ces infections, en particulier pour les micro-organismes non cultivables ou difficiles à cultiver par les méthodes classiques de laboratoire.

Cette étude met en lumière les évolutions majeures de l'épidémiologie microbiologique des péritonites liées à la dialyse péritonéale en France, sur une période couvrant plus de quatre décennies, à partir des données issues de plus de 20 000 patients inclus dans le RDPLF, et ce à la lumière des progrès technologiques récents.

Mots-clés : dialyse péritonéale, infection, péritonite,microbiologie

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Introduction

The prevalence of chronic kidney disease is currently estimated at 8-10% of the French population, with the total number of dialysis and transplant patients rising sharply (+25%) between 2012 and 2020 [1, 2]. In France, the use of the peritoneum as a dialysis membrane for treating these patients dates back to the 1950s, with the introduction of intermittent peritoneal dialysis (IPD), followed in the late 1970s by continuous ambulatory peritoneal dialysis (CAPD), and finally automated peritoneal dialysis (APD) in the 1980s. The use of APD or CAPD facilitates patient autonomy and is an alternative to hemodialysis [3]. One of the main complications of these techniques is infection, and peritonitis is the most frequent cause of discontinuation of peritoneal dialysis, associated with significant morbidity and mortality [4]. Nevertheless, while the frequency of peritonitis was on the order of one episode every 2 to 3 months in the early 1980s, it is now on the order of one episode every 2 to 5 years [5]. The prevalence of these infections and the bacteria associated with them varies greatly between care centers, even within the same country, making comparisons between them difficult to interpret [6, 8]. The Registre de Dialyse Péritonéale de Langue Française (French-Language Peritoneal Dialysis Registry, RDPLF) database brings together data from patients treated with home peritoneal dialysis since the early 1980s in several French-speaking countries. Over the last five decades, major technical developments have taken place concerning peritoneal dialysis and associated equipment on the one hand and microbiological analyses on the other. Here, we present the microbiological changes observed in peritonitis associated with peritoneal dialysis from the 1980s to the present day, using data from more than 20,000 patients and in light of these technological advances.

Materials and methods

This is a retrospective multicenter study based on data from the RDPLF.

Using the REIN registry, which is managed by the Agence de Biomédecine in France, as a reference, the completeness of the RDPLF is currently estimated to cover more than 90% of all patients treated with peritoneal dialysis in France.

The inclusion period was from July 1978 to February 2023, and only French data were included. Events corresponding to peritonitis in patients receiving peritoneal dialysis were selected.
Peritonitis cases without peritoneal dialysate sampling, occurring after cessation of peritoneal dialysis, of non-infectious cause, or without microbiological documentation were excluded.

The following data were collected: sex, age, region of care, presence of diabetes, date of start of dialysis, type of dialysis, date of onset of peritonitis, and bacteria detected.

The proportions of episodes corresponding to the variables of interest were analyzed by Fisher's exact test or the chi-square test with alpha set at 0.05. Comparisons of age between populations or dialysis durations were made with a parametric one-way ANOVA test with alpha set at 0.05.
The calculations were performed using GraphPad Prism software version 10.5.0 (GraphPad Software).

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Results

1. Extraction of results

A total of 32,503 episodes were extracted from the RDPLF. Among these, 328 episodes were excluded for a lack of dialysate sampling, 304 for inconsistent time to onset of peritonitis, 146 for documented non-infectious cause, and 5387 for lack of microbiological documentation.
A total of 26,325 peritonitis events corresponding to 20,479 patients were included *(Figure 1)*.

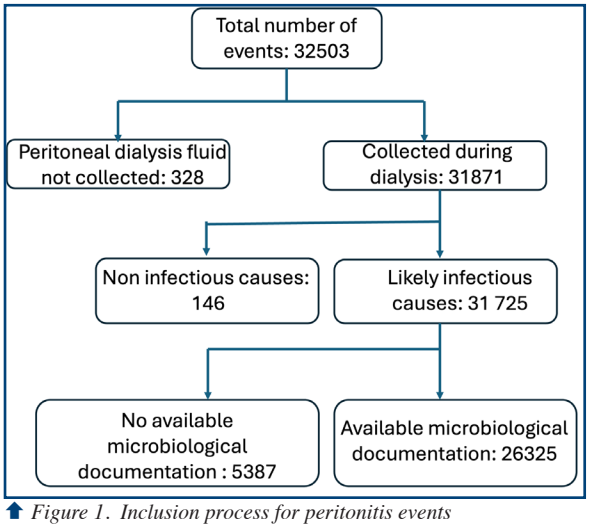

Figure 1. Inclusion process for peritonitis events

2. Population analysis

The main characteristics of the cohort population (age, number of patients, comorbidities, etc.) are summarized in *Table I*. The sex ratio was 1.4, and there were four times more documented first episodes of peritonitis than recidives. The presence of diabetes as a comorbidity was found in 12% of patients, irrespective of gender. The median time to onset of peritonitis rose from around 12 months in the 1970s to over 35 months in the 2010s *(Figure 2)*. The median age of onset of peritonitis also changed over the decades, rising from around 50 years in the 1970s to 70 years in the 2010s *(Figure 3)*, but no significant difference was observed between first episodes of peritonitis and recidives. The median age of onset was nevertheless significantly earlier in the female population (*Figure 4A*; p<0.0001). The other factor influencing the age of onset of infectious episodes was the type of peritoneal dialysis, with a significantly higher age in the population managed by CAPD compared to APD (p<0.0001) (*Figure 4B*).

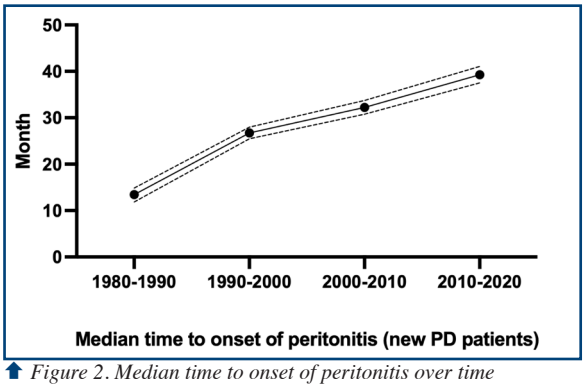

Figure 2. Median time to onset of peritonitis over time

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Table I. Characteristics of the cohort

	Male	Female
Number of patients	11,768	8711
Number of episodes of 1st peritonitis	20,479	
Number of peritonitis recidives	3414	2432
Diabetes	1404	1073
Peritonitis on dialysis after transplant rejection	780	
	Median	
Age of patients at time of peritonitis	69 (25th to 75th percentiles: 57; 78)	68 (25th to 75th percentiles: 55; 78)
Age at time of peritonitis before 1980	53 (25th to 75th percentiles: 50; 71)	
Age at peritonitis 1980-1989	61 (25th to 75th percentiles: 57; 76)	
Age at onset of peritonitis 1990-1999	68 (25th to 75th percentiles: 57; 79)	
Age at onset of peritonitis 2000-2009	71 (25th to 75th percentiles: 57; 79)	
Age at onset of peritonitis 2010-2019	70 (25th to 75th percentiles: 57; 80)	
Age at peritonitis 2020 and later	70 (25th to 75th percentiles: 59;78)	

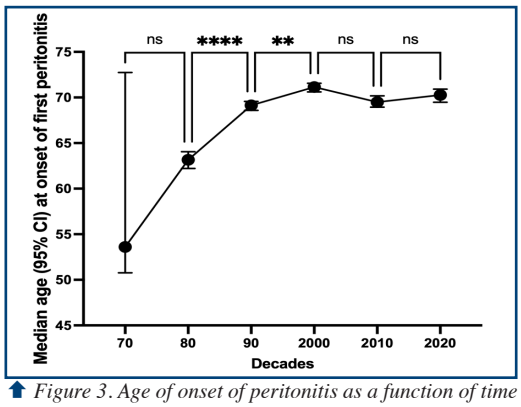

Figure 3. Age of onset of peritonitis as a function of time

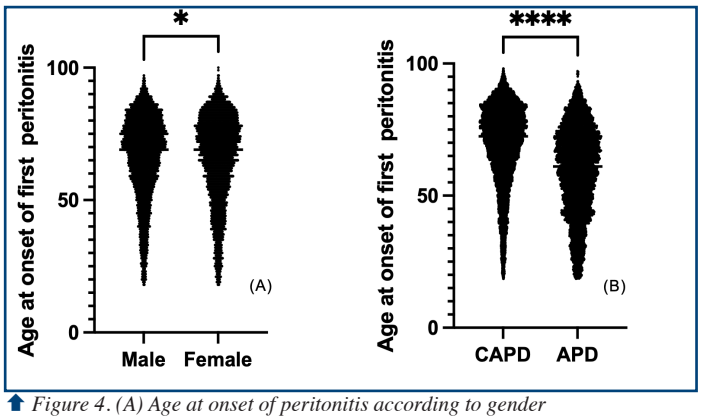

Figure 4. (A) Age at onset of peritonitis according to gender
(B) Comparison of age at onset of 1st peritonitis between DPCA and DPA

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3. Frequency of use of dialysis techniques

Different peritoneal dialysis techniques have been used over the last 45 years *(Figure 5)*. The predominant technique remains CAPD, accounting for 100% of our cohort in the 1970s-1980, followed by APD, which made a discreet appearance in the 1990s (around 10%), then democratized to reach around 40% between 2010 and 2020. Management of patients by APD or mixed APD/CAPD dialysis remained anecdotal.

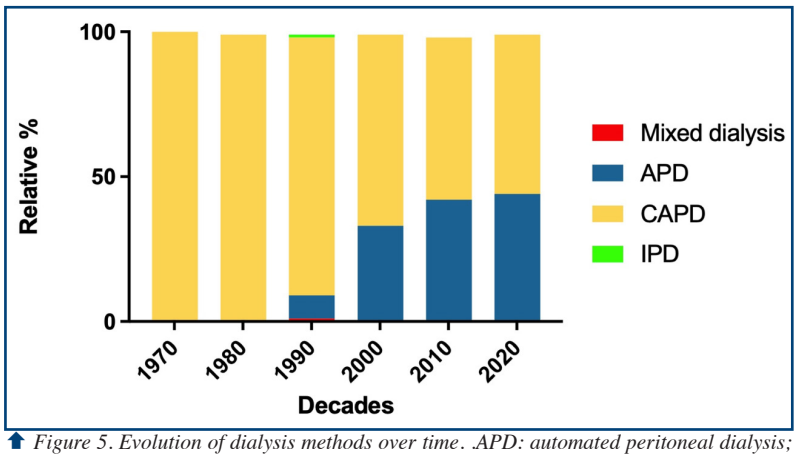

Figure 5. Evolution of dialysis methods over time. APD: automated peritoneal dialysis; CAPD: continuous ambulatory peritoneal dialysis; IPD: intermittent peritoneal dialysis

4. Microbial epidemiology

Firstly, the bacteria responsible for infections in peritoneal dialysis, whatever the technique used, are the same *(Figure 6A)*. Among the most frequent are *staphylococci (S. aureus and non-aureus)*, *Streptococcus*, and E*nterobacteria*. All the bacterial genera referred to as non-fermenting Gram-negative bacilli and Gram-positive bacilli are detailed in *Table S1*. However, there are significant differences in the proportion of these bacterial genera depending on the peritoneal dialysis technique used. Thus, coagulase-negative staphylococci (CNS) and streptococci infections are over-represented in patients managed by CAPD compared with APD (p<0.0001). Conversely, non-fermenting Gram-negative bacilli, Gram-positive bacilli, enterobacteria, enterococci, *S. aureus,* and polymicrobial infections were more frequent in the APD arm (p<0.0001). The proportion of anaerobic bacterial infections was identical in both groups.

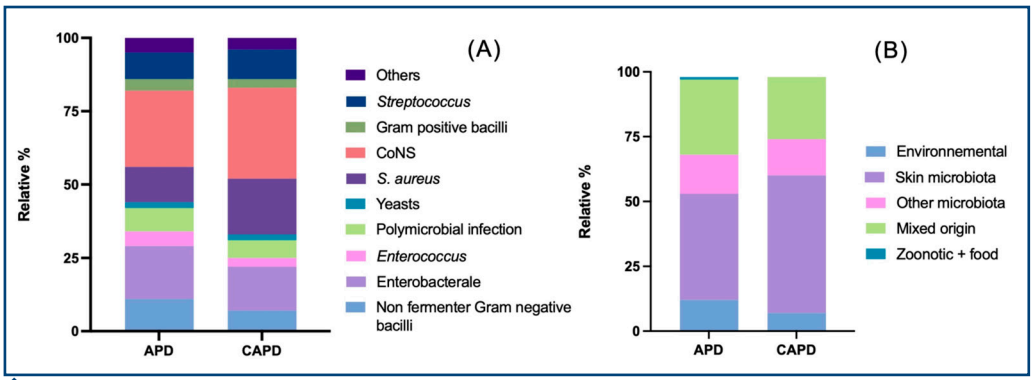

Figure 6. (A) Proportions and origins of species responsible for peritonitis in the APD and CAPD groups. (B) Proportions and origins of germs responsible for peritonitis in the APD and CAPD groups

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All these bacteria can be classified according to their natural ecology, whether environmental, cutaneous, oral/digestive, or zoonotic and foodborne *(Figure 6B)*. All bacterial genera sorted according to their ecological origin are detailed in Table S2. Analyzing these data, species of cutaneous origin were more frequently encountered in CAPD than in APD infections (p<0.0001), while bacteria of environmental and mixed (oral/digestive) origin were over-represented in the APD arm (p<0.0001). These differences were maintained when analyzing the male and female subgroups.

5. Evolution of microbial epidemiology over the decades

The distribution of infection-causing bacteria over time is shown in *Figure 7*. While some bacterial genera saw their proportion decrease between the 1970s and 2020 (*S. aureus*, coagulase-negative staphylococci (CoNS)), others saw their frequencies increase over the same period (Enterobacteriaceae, enterococci, streptococci, and polymicrobial infections) (p<0.0001). For non-fermenting Gram-negative bacilli, a fluctuation is observed, with a decrease between the 80s and 90s, followed by an increase between 1990 and 2000. The evolution of these distributions is unchanged when analyzing the CAPD and APD subgroups (data not shown).

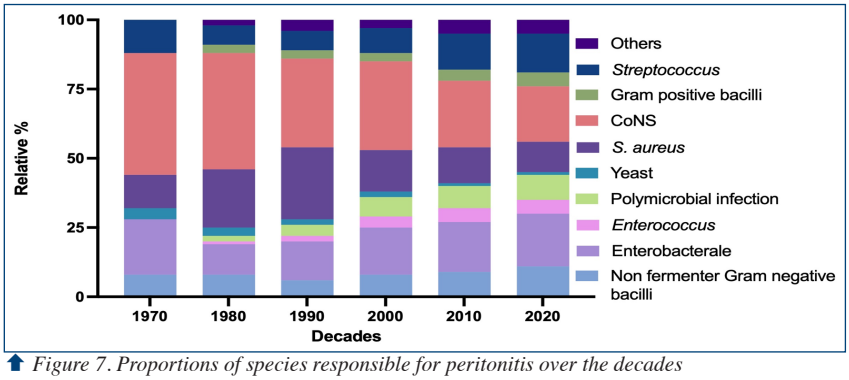

Figure 7. Proportions of species responsible for peritonitis over the decades

6. Evolution of microbial epidemiology as a function of patient age

Analysis of the bacteria responsible for peritonitis as a function of patient age shows that non-fermenting Gram-negative bacilli and *S. aureus* infections are more frequent in people under 50, while Enterobacteriaceae, enterococci, and polymicrobial infections increase steadily with patient age (p<0.0001) *(Table II)*.

Table II. Trends in the frequency of infection-causing microorganisms as a function of patient age

		Non-fermenting Gram-negative bacilli	Enterobacteria	Enterococcus	Polymicrobial infection	S. aureus	CoNS
APD	<50 years old	11.22%	15.75%	4.27%	7.67%	16.71%	25.14%
	50 to 79 years	11.38%	18.79%	4.70%	8.33%	10.92%	26.13%
	>80 years	9.37%	20.75%	6.63%	9.51%	8.21%	26.66%
CAPD	<50 years	8.17%	11.37%	1.31%	3.58%	26.54%	30.75%
	50 to 79 years	6.72%	14.59%	2.63%	5.36%	19.31%	32.08%
	>80 years	6.08%	18.62%	4.32%	7.64%	15.93%	28.55%

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When only the APD or CAPD populations are studied, these phenomena are identical, except in the specific case of APD, where the frequency of non-fermenting Gram-negative bacilli infections does not decrease significantly with age.

7. Dialysis duration and microorganism responsible for peritonitis

The frequencies of microorganism involvement were analyzed as a function of the duration of dialysis before infection occurred *(Figure 8)*. It appears that CoNS infections occur statistically later (around 30 days) than the average (p=0.0084), while S. aureus infections occur earlier by around 50 days (p=0.0004). This distribution is independent of the type of dialysis used.

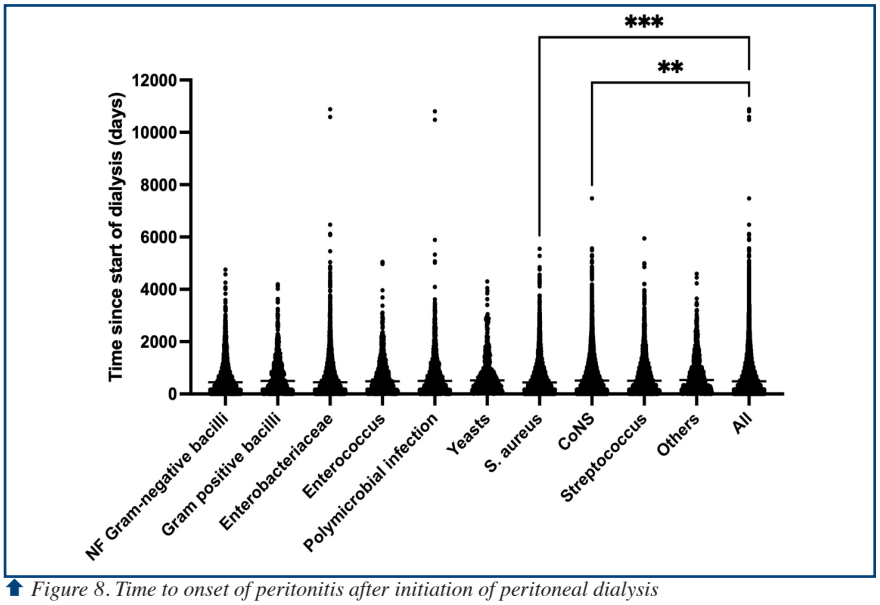

Figure 8. Time to onset of peritonitis after initiation of peritoneal dialysis

8. Recidives

Comparing microbiological data obtained in first episodes of peritonitis versus recidives, we found a significantly higher frequency of Enterobacteriaceae, Streptococcus, and polymicrobial peritonitis in first episodes (p=0.0001), whereas recidives were more often associated with yeast and CoNS infections (p=0.0001, p=0.0001) *(Figure 9)*. In the dialysis population after transplant rejection, the rate of peritonitis recurrence (15.76%) was significantly lower than in the rest of the population (22.4%; p<0.0001).

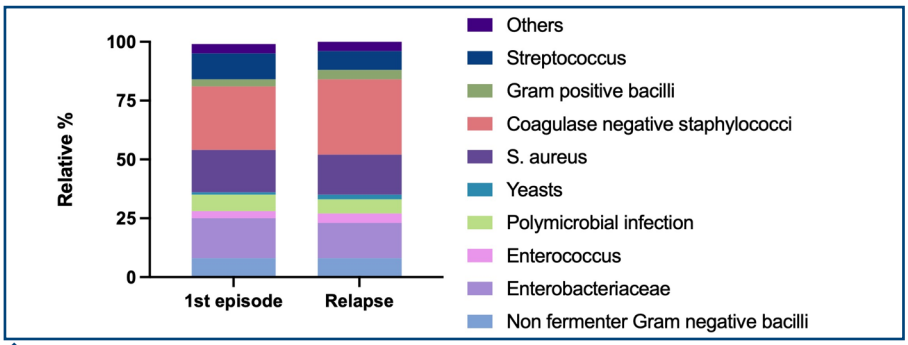

Figure 9. Proportions of species responsible for peritonitis for 1st episodes and recidives.

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Discussion

Analysis of the RDPLF microbiological database over a 40-year period retraces part of the history of peritoneal dialysis in France. As with any database, there is room for improvement, since all the data are deposited voluntarily, and these deposits evolve over time, with the appearance of new centers and/or new data collected (incidence data, comorbidities, new bacterial species, new clinical definitions, etc.), making their analysis complex. What's more, the data obtained from these different dialysis centers are themselves very difficult to compare, as the implementation of new techniques, new equipment, and new protocols inevitably takes place at different times in different centers. Clearly, not all facilities work in the same way at any given time. These difficulties have therefore led us to make three conscious choices: (1) to use only metropolitan French data and not those of other French territories or French-speaking countries, in order to limit variability as much as possible; (2) not to analyze data according to the different types of dialysis center; and (3) to analyze these data in relation to each other, and not in absolute values.

Despite these choices, the results obtained remain interesting to discuss. Firstly, and unsurprisingly, the germs found to be responsible for peritonitis in peritoneal dialysis in France over the past 45 years are no different from those observed in the literature [6, 8]. The most frequent germs are staphylococci, represented in over 50% of infections, followed by streptococci and enterobacteria. The distribution of infection-causing bacteria varies according to the dialysis technique used. Specifically, germs belonging to the skin flora (mainly CoNS and *S. aureus*) were over-represented in patients receiving CAPD. The multiple daily manipulations associated with CAPD dialysis cycles could lead to a greater risk of catheter colonization by these germs compared with APD, but this explanation remains to be scientifically proven. *S. aureus* infections are also over-represented in younger populations under 50. This could be explained by a higher carriage of S. aureus in these populations than in older populations [9, 10]. For the populations over 50, *S. aureus* infections tend to decrease, giving way to infections by germs of digestive origin, such as enterobacteria or polymicrobial infections. The origin of these infections is said to be endogenous and is correlated with a higher incidence of gastrointestinal pathologies in older populations [11]. Another independent risk factor has also been described in this older population, where the duration of hypokalemia greatly increases the prevalence of peritonitis [12], and in particular that of Enterobacteriaceae [13]. The frequent use of proton pump inhibitors in these patients also increases the risk of peritonitis [14]. The delay in the onset of peritonitis also appears to be correlated with the identified bacteria: *S. aureus* infections have an earlier onset than CoNS infections. The greater pathogenic power of *S. aureus* compared to CoNS would make the symptomatology of these peritonitis cases more acute and therefore possible to detect earlier. In addition, nasal carriage of *S. aureus* facilitates hand-carried contamination, and is recommended for certain types of surgery [15].

Beyond these data, which are fairly well documented in the literature, the evolution of the germs found over time is of interest. The proportion of staphylococcal infections fell drastically between 1970 and 2010. While part of the explanation lies in the aging of the peritoneal dialysis population, as discussed above, the evolution of connectology and the use of dialysis solutions with improved biocompatibility are probably at the origin of this observation [16], as well as the widespread use of hydroalcoholic solutions for hand disinfection. At the same time, the proportion of infections linked to germs of endogenous origin has increased, particularly in older populations.

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The contribution of the new microbiology techniques has not been clearly demonstrated, but the proportion of peritonitis cases with no germs found shows significant inter-center variability, due as much to the practices of the center itself as to those of the laboratory attached to it [17]. Nevertheless, certain bacterial genera detected, such as Chlamydiaceae or Oscillospiraceae, could only be identified thanks to the contribution of molecular biology. Recent publications using high-throughput sequencing techniques on samples will undoubtedly bring their share of new identifiable pathogens in the coming years, thus improving the diagnosis and management of these peritonitis cases [18, 19].

Conclusion

The microbiology of peritonitis in peritoneal dialysis has evolved considerably over the last 50 years. These changes result from a number of factors, linked on the one hand to the population and on the other to dialysis techniques and equipment. The coming decades will undoubtedly bring changes to this particular epidemiology.

In light of recent technological advances in dialysis techniques and microbiological identification techniques, this study highlights major developments in the microbiological epidemiology of peritonitis associated with peritoneal dialysis in France over a period of more than four decades, based on data from over 20,000 patients included in the RDPLF.

Authors' Contributions

FB wrote the article and performed the statistical analysis, FH and LB reviewed the article, provided comments and corrections, AG promoted the study and reviewed and corrected the work.

Ethics statement

The RDPLF database is registered with the French National Commission for Information Technology and Civil Liberties under number 542668. The data was extracted after being completely anonymized using a random hash key that was destroyed after use.

Funding

The authors did not receive any funding for this work.

Conflicts of Interest

The authors declare that they have no conflicts of interest with this study.

Data availibility statement

The datasets generated during the current study are available from the RDPLF secretariat upon reasonable request.

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Supplemental material

Table S1. Bacterial subgroups

Non-closing Gram-negative bacilli	Gram-positive bacilli
Alcaligenaceae	Bacillaceae
Brucellaceae	Brevibacteriaceae
Burkholderiaceae	Carnobacteriaceae
Caulobacteraceae	Corynebacteriaceae
Comamonadaceae	Lactobacillaceae
Flavobacteriaceae	Nocardiaceae
Moraxellaceae	Paenibacillacaea
Pseudomonadaceae	Propionibacteriaceae
Sphingomonadaceae	
Xanthomonadaceae	

Table SII. Microorganisms and their reservoirs

Environmental	Cutaneous	Oral/digestive	Zoonotic + foodborne
Aeromonadaceae	Acetobacteraceae	Actinomycetaceae	Campylobacteriaceae
Alcaligenacaea	Corynebacteriaceae	Aerococcaceae	Listeriaceae
Bacillaceae	Yeasts	Enterobacteriaceae	Pasteurellaceae
Brevibacteriaceae	Micrococcaceae	Bacteroidaceae	Streptococcaceae
Brucellaceae	Propionibacteriaceae	Carnobacteriaceae	Yerciniaceae
Burkholderiaceae	Staphylococcaceae	Chlamydiaceae	
Caulobacteraceae		Enterococcaceae	
Filamentous fungi		Flavobacteriaceae (Capnocytophaga spp)	
Clostridiaceae		Fusobacteraiaceae	
Comamonadaceae		Hafniaceae	
Erwiniacaeae		Lactobacillaceae	
Flavobacteriaceae		Yeasts	
Microbacteriaceae		Moraxellaceae	
Moraxellaceae (Acinetobacter spp)		Morganellaceae	
Nocardiaceae		Neisseriaceae	
Paenibacillacaea		Oscillospiraceae	
Phyllobacteriaceae		Pasteurellaceae	
Pseudomonadaceae		Peptostreptococcaceae	
Rhizobiaceae		Streptococcaceae	
Rhodobacteriaceae			
Sphingomonadaceae			
Xanthomonadaceae			

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