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REVIEWS

A QUALITATIVE SYSTEMATIC REVIEW OF THE LITERATURE SUPPORTING A CAUSAL RELATIONSHIP BETWEEN EXIT-SITE INFECTION AND SUBSEQUENT PERITONITIS IN PATIENTS WITH END-STAGE RENAL DISEASE TREATED WITH PERITONEAL DIALYSIS

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♦ ***Objective:*** **The objective of our research was to summarize and review evidence supporting a causal relationship between exit-site infection and peritonitis in peritoneal dialysis (PD) patients.**

♦ ***Data Sources:*** **We undertook a qualitative review of studies retrieved from MEDLINE, EMBASE, and PubMed, and supplemented that process with a hand search of references and abstracts in the literature.**

♦ ***Study Selection:*** **Our quality criteria were based on the Paediatric Risk of Mortality guidelines, definitions, and recommendations from the International Society for Peritoneal Dialysis (ISPD), and the Bradford Hill criteria for causality. All identified abstracts were reviewed for content. Of 776 abstracts, 59 were selected for full-text evaluation, and 22 of those met the ISPD criteria for good-quality research in PD-related infections. Of the 22 eligible studies, 9 met the study's quality criteria and were included in the summative analysis. No articles reported sufficient data for a quantitative analysis.**

♦ ***Data Extraction:*** **Information on study design, study population characteristics, definitions, peritonitis rates, exit-site care protocol, exit-site treatment protocol, follow-up period, potential bias, and outcomes was extracted. Criteria for including data in the final study were determined using ISPD guidelines.**

♦ ***Data Synthesis:*** **Of the 9 included studies, 8 suggested that a history of exit-site infection increased the risk for subsequent peritonitis. Of those studies, 3 met 5 causality criteria, 4 met 4 causality criteria, and 1 met 3 causality criteria.**

♦ ***Conclusions:*** **The literature provides weak evidence to support a causal relationship between exit-site infection and subsequent peritonitis. Few criteria for causation were met. We were unable to attribute causation and could assume an association only. The exclusion of studies focusing on PD-related tunnel infections may be viewed as both a strength and a limitation of the present work.**

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KEY WORDS: Exit-site infection; catheter infection; peritonitis; infectious complications; causality; Bradford Hill.

Catheter-related infections are the most common, and serious, of all complications associated with chronic peritoneal dialysis (PD). Although infection rates have declined in recent years, bacterial and fungal infections continue to be the leading cause of technique failure and mortality in PD patients (1–7).

It has long been assumed that a bacterial (or fungal) infection around the catheter exit site ["exit-site infection" (ESI)] will lead to tracking along the catheter path and a predisposition to peritonitis. As a result, the International Society for Peritoneal Dialysis (ISPD) and other leading authorities have recommended measures to help prevent, detect, and aggressively treat ESIs (3–7). We questioned whether the literature supports only a clinical association between ESI and peritonitis or whether the data are sufficient to establish causality. The distinction is important to those interested in developing novel or innovative strategies to reduce the incidence of peritonitis, particularly if aggressive strategies to

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reduce or manage ESIs inadvertently increase the risk of peritonitis by an alternative mechanism.

In the present study, we used robust epidemiologic criteria (Bradford Hill criteria) to make a distinction between causation and association (8). The Bradford Hill criteria outline the conditions that should ideally be fulfilled to establish a causal relationship between two events. In the absence of those criteria, an association only and not causality must be assumed.

Association and causation are epidemiologic concepts. The term "association" describes any relationship between 2 or more variables without attributing cause and effect. Such variables might be associated indirectly through other important characteristics of the patient or the environment. In contrast, the term "causation" implies that changes in (or exposure to) variable *A* directly causes changes in variable *B*. In medicine, causation can rarely be proven; however, certain characteristics can be sought to support causality.

The objective of the present study was to systematically review the literature and to summarize the evidence supporting a causal relationship between ESI and peritonitis.

METHODS

We used a 3-step process: literature search, data quality assessment, and data extraction.

LITERATURE SEARCH AND ELIGIBILITY CRITERIA

We undertook a literature search with the help of a specialist librarian. Three medical databases (MEDLINE, EMBASE, PubMed) were systematically searched, and relevant reference lists and published abstracts were subsequently hand-searched (Figure 1). Search terms included "peritoneal dialysis" AND "peritonitis" AND 1 of 3 terms associated with ESIs ["catheter-related infections" OR "catheterization/ae" OR "(exit site adj4 infection*).mp"]. Determination of tunnel infections was felt to be highly dependent on both screening and diagnostic protocols within units, and therefore "tunnel infection" was not included as a search term. All identified abstracts were screened, and selected full texts were reviewed to ensure that they met the eligibility criteria: inclusion of information about ESIs and peritonitis, and specificity to PD patients.

DATA QUALITY ASSESSMENT

Eligible studies underwent a quality assessment using criteria specific to our question. The criteria were developed in two steps. In the first step, we used the ISPD definitions of good-quality research on PD-related infections (Table 1) to determine criteria for "adequate quality" (5). We then identified which question-specific data elements were required to meet each of the 9 Bradford Hill criteria for causation (8) (Table 2).

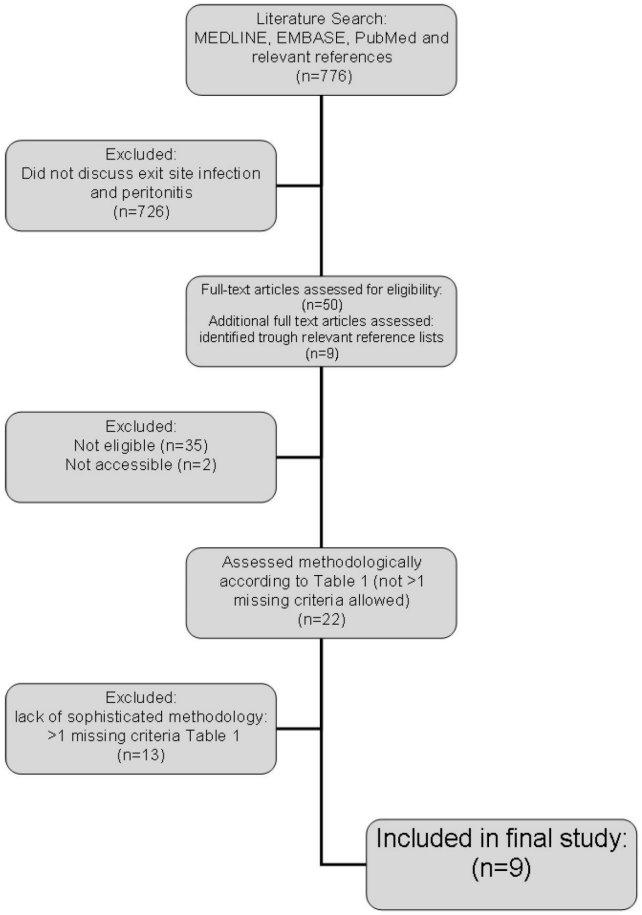

Figure 1 — Literature search.

DATA EXTRACTION

In the final step, demographic data, publication data, and risk results were all extracted using a systematic approach. All data were extracted by a single observer (ATNVD).

RESULTS

IDENTIFICATION OF QUALITATIVE EVIDENCE

The literature search found a total of 776 papers. Reference lists were hand-searched and an additional 9 papers were identified. We excluded 726 papers because they did not report data pertaining to both ESIs and

TABLE 1
Variables for Quality Assessment of the Literature Reporting a Relationship Between Exit-Site Infection and Peritonitis

Manuscript should include:

- Baseline characteristics
  - Study design (for example, prospective, retrospective)
  - Study population (inclusion and exclusion criteria)
  - Population age, sex, race, percentage of diabetic patients
  - Follow-up duration (to include follow-up period and methodology for collecting information)
- Clear definitions of exit-site infection and peritonitis that are consistent with ISPD guideline recommendations.
- Clear definitions of recurrent and relapsing peritonitis that are consistent with contemporary ISPD guideline recommendations.
- Sufficient data to calculate peritonitis rates as episodes/patient–year (overall and for individual organisms, as applicable) or the use of time to peritonitis.
- Clear description of the exit-site care protocol (for example, use of prophylaxis, eligible recipients).
- Clear description of the treatment of exit-site infection (for example, was it protocol-based or left to physician discretion).

ISPD = International Society for Peritoneal Dialysis.

peritonitis rates. Papers focusing solely on tunnel infections or nasal carriage were excluded (9–14). We assessed the full texts of the remaining 59 articles for eligibility. After assessment, an additional 37 papers were excluded because they did not contain information relevant to the relationship between ESIs and peritonitis.

Table 2 sets out our criteria for adequate quality. Those criteria were applied to all 22 papers (15–36) that reported relevant information. Among those 22 papers, only 9 (15–23) met sufficient criteria to be included in the final analysis (Figure 1, Table 1).

STUDY CHARACTERISTICS

Table 3 summarizes the baseline characteristics of the 9 studies. Although all the studies reported peritonitis rates (range: 0.38 – 1.36 episodes per patient–year), only 5 of the 9 (19–23) met the reporting standards recommended by the ISPD guidelines (5). The incidence of ESI varied broadly between studies, with an overall trend of declining rates over time: studies published before 1990 reported 1.02 episodes per patient–year (15,16), and studies from subsequent years reported 0.20 – 0.80 episodes per patient–year (17–23).

BRADFORD HILL CRITERIA FOR CAUSATION

Of the 9 studies (15–23) that met our criteria for a full qualitative review, 8 (15–17,19–23) reported a temporal relationship between ESI and peritonitis, and 1 study (18) reported no relationship between ESI and recurrent or relapsing peritonitis. Table 3 shows the results of the quality assessment.

The criterion of biologic feasibility was considered fulfilled because it is widely accepted that organisms can track along implanted devices. In PD patients, the organisms would track along the catheter wall between the exit site and the peritoneum. Clear evidence of a temporal relationship was missing in 3 reports (16,19,22) that did not have a clear definition of ESI-related peritonitis. In those 3 studies, it was unclear whether peritonitis preceded, occurred simultaneously with, or presented after ESI. Sufficient data were given in 5 studies (15–17,21,23) to allow for derivation of the relative risk ratio of peritonitis after ESI compared with peritonitis without ESI (range: 1.4 – 6.3). Other studies (18–20,22) did not include sufficient data for a calculation of a risk ratio from their results. Only 1 study reported whether an individual's hazard of peritonitis declined over time (23).

Causation criteria suggest that other possible explanations for the identified relationship should be sought and, to establish causality, excluded. Of the studies reviewed, 7 (15,17,19–22,23) discussed other explanations for the relationship, but were unable to support or refute the relative importance of those explanations. The study by Lee *et al.* (20) controlled for the overrepresentation of patients with diabetes in their population. Only 1 study (16) did not discuss any alternative conclusions.

Any intervention that has an impact on one variable and effects a change in another (for example, a treatment that reduces the incidence of ESI that reduces peritonitis) can support a determination of causality between ESI and subsequent peritonitis. In 2 studies (17,22), an intervention may have affected the ESI incidence. In one of those studies (17), the authors reported results before and after the introduction of the Y-set in combination with an intensified antibiotic treatment protocol for ESI; in the other (22), the exit-site prophylaxis protocols were changed. Both studies showed a decline in both the ESI rate and the peritonitis rate, suggesting causality. (Ideally an attempt would have been made to withdraw therapy and see a return to baseline infection rates, but taking that action was not feasible.)

TABLE 2
Quality Assessment Based on the Principles of the Bradford Hill Criteria for Causation

	References without available data	References fulfilling the criterion			
		Yes	No	(*n*)	Conclusion
Temporality	15,17,18,20,21	23	16,19,22	1	Literature did not report on the temporal relationship between ESI and peritonitis.
Strength	18–20,22	15–17,21,23	—	5	Only some literature supported the identified relationship between ESI and peritonitis with a risk ratio.
Biologic gradient	15–23	—	—	0	Data to determine the gradual biologic influence of ESI leading to an increased incidence of peritonitis were unavailable.
Analogy	16	20	15,17–19,21–23	1	Most literature concerning the relationship between ESI and peritonitis was unable to refute other explanations for the reported relationship.
Experiment	15,16,18–21,23	17,22	—	2	Literature reporting an intervention during follow-up showed a reduction in ESIs, which led to a reduction in the incidence of peritonitis.
Biologic plausibility	—	15–23	—	9	Literature supports the biologic plausibility of an ESI's leading to peritonitis.
Specificity	—	—	15–23	0	Literature was unable to eliminate confounding factors with an effect on the relationship between ESI and peritonitis.
Consistency	—	15–17,19–23	18	8	The relationship between ESI and peritonitis was seen in various study populations and settings worldwide.
Coherence	—	15–23	—	9	Literature supporting the relationship between ESI and peritonitis is compatible with current clinical knowledge and existing theory.

ESI = exit-site infection.

Overall, the literature was consistent across the various study populations and study settings. Because 4 studies did not report the strength of the observed association, consistency across the estimated risk was not established. Nor was it possible to comment on the presence or absence of a biologic gradient (akin to dose–response) by searching for a graduated risk in either the number of ESIs or the risk attribution.

DISCUSSION AND CONCLUSIONS

We used the Bradford Hill criteria for causation (8) to evaluate whether the literature was able to establish causality between ESI and subsequent peritonitis. According to our strict qualitative review, the data supported an association, but were insufficient to demonstrate a causal relationship. The presence of an association questions (a) whether the relationship depends on the individual (a patient with an ESI has an inherent immunologic risk, placing him or her at higher risk of peritonitis) or (b) whether the ESI itself directly compromises the patient and predisposes the individual to a newly increased risk of peritonitis. We believe that the answer is important because it can inform the development of novel strategies to reduce peritonitis. If the answer is (a), then novel strategies will target

TABLE 3
Characteristics of Included Studies

Reference	Design	Pts (*n*)	Age (years)	Follow-up (per patient)	Country	Definition of ESI-related peritonitis	Reported relationship	Strength
Piraino *et al.*, 1986 (15)	Prospective	137	50±15 (19–81)	15.0±9.6 months (3–46 months)	USA	NA	Yes	1.42
Piraino *et al.*, 1987 (16)	Prospective	137	50±15 (19–81)	15.0±9.6 months (3–46 months)	USA	≤2 weeks	Yes	1.42
Lee and Woo, 1992 (20)	Prospective	130	51±13 (7–77)	Maximum 1 year	Singapore	NA	Yes	NA
Gupta *et al.*, 1996 (22)	Partly prospective	512	48±15 (35–65)	From ESI or peritonitis to catheter removal	USA	≤2 weeks	Yes	NA
Paquay *et al.*, 1996 (17)	Partly prospective	118	43 (17–84)	17 months (2 days–73 months)	Holland	NA	Yes	1.54
Crabtree and Siddiqi, 1999 (19)	Prospective	57	49.6 (15–78)	From catheter implantation to max. end of study	USA	≤4 weeks	Yes	NA
Szeto *et al.*, 2007 (18)	Retrospective	152	52.3±13.5 NA	From peritonitis to at least 3 months after completion of antibiotics	China	NA	No	NA
Lobo *et al.*, 2010 (21)	Retrospective	330	53±19 NA	At least 20 days to max. end of study	Brazil	NA	Yes	2.6
Van Diepen *et al.*, 2012 (23)	Prospective	203	60±14 (23–100)	18 months (0.1–18.0 months)	Canada	≤30 days	Yes	6.32

NA = data not available; ESI = exit-site infection.

identification of the patient at risk and apply patient-level interventions; if the answer is (b), novel treatments will target ESI prevention.

We were surprised to find that the literature did not establish a causal relationship between ESI and subsequent peritonitis. We suggest that further work is required in the field. We recommend wider adoption of the recent ISPD guidelines for research into infections (5) and the strict inclusion of a time interval in papers reporting an association between ESI and any related peritonitis episodes. Published articles should include a clear definition of ESI-related peritonitis, support the results with a numeric estimate of the risk strength, and distinguish between ESI and tunnel infection if possible. We also raise the question of whether, as PD physicians, we need to reconsider the correctness of the assumption that ESI leads directly to subsequent peritonitis and to investigate phenotype in patients in whom ESI leads to subsequent peritonitis. Researchers might then be able to identify the nature of important contributing factors.

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DISCLOSURES

In the past 3 years, SVJ has received speaker honoraria from Amgen Canada.

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