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Emphysematous pyelonephritis

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ABSTRACT

Emphysematous pyelonephritis (EPN) is an acute severe necrotizing renal infection with serious features. In the absence of efficient treatement, it leads to significant morbidity and mortality due to septic complications. In the literature , it is estimated that 95% of the cases with EPN have underlying uncontrolled diabetes mellitus, and about 25–40% the risk of developing EPN secondary to a urinary tract obstruction. There are three classifications of EPN based on radiological findings. However, acute renal failure, microscopic or macroscopic haematuria, severe proteinuria are other objective positive findings in EPN. Escherichia coli is the most causative pathogen. It is found in 70% of cases with the organism isolated from urine or pus cultures. A standard KUB (Kidney-ureter- bladder) which shows an abnormal gas shadow ing the renal bed, is an alarming element, whereas anultrasound or CT scan of the abdomen will confirm EPN diagnosis. It should be noted that the gas can extend beyond the site of inflammation to the subcapsular, perineal and pararenal spaces. In some cases, it was found that the gas extended into the scrotal sac and the spermatic cord. The treatment strategies include MM alone, PCD plus MM, MM plus emergency nephrectomy, and PCD plus MM plus emergency nephrectomy. Several studies have shown patients being successfully treated with PCD when used in combination with medical management, leading to significant decrease in the morality rates. PCD should be performed on patients who have localized areas of gas. Few patients who received MM and PCD, subsequently required nephrectomy. It is important to note that nephrectomy in patients with EPN can be simple, laparoscopic or radical.

Keywords: Emphysematous pyelonephritis, diabetes mellitus, escherichia coli, percutaneous drainage,

Introduction

The emphysematous pyelonephritis is clinically described for the first time in 1898 by Kelly and MacCallum. From this date words such as « renal emphysema », « pneumonephritis » as well as « emphysematous pyelonephritis » have been used to qualify the gas-forming infection.

However its actual denomination has been suggested by Schultz and Klorfein [1, 2, 3, 4].

The non-specific characteristics of the clinical picture and the absence of a strict definition of of this infection often lead to a delay in the diagnosis, thus leading to different medical interventions. However, this is a necrotic infection of the kidney, which is characterized by the presence of gas at the level of the renal parenchyma, the excretory cavities or the peri-renal spaces. [3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14].

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Severe EPN is life-threatening through a septic shock state and is characterized by high mortality rates varying between 40 and 50% [14, 15, 16, 17, 18]. Although it usually occurs in uncontrolled diabetic patients – insulin dependent or not – it is also found among patients presenting a urethral obstruction and/or immuno-compromised [3, 19, 20, 21, 22, 23]. Its prevalence is predominantly among women [2, 3, 4]. Indeed, the studies [13, 24] report a female: male gender ratio of 4:1 and a mean age of 57 (24-83) years. The ones led by Michaeli and al. and A. Derouiche and al [22, 25], report respectively as for them a gender ratio of 1/1,8 (64% of females and 36% of males) and a sexratio of one third, approximately 15 females Vs 6 males. Computed tomography (CT) remains the gold standard diagnostic tool [22].
This one enables to elucidate the diagnosis, to evaluate the prognosis and to choose the best therapeutic behaviour [25, 26, 27, 28, 29].
However, we can notice the absence of any consensus regarding the therapeutic approach.
So, the treatment of the EPN is either based on antibiotic therapy, associated, according to the presence or not of criteria of bad prognosis, with either percutaneous drainage or endo-urethral drainage, or a nephrectomy [24].
Whereas several works advise that the EN (Emergency Nephrectomy) must be the corner stone of the therapeutic process and should be immediately considered whatever the situation [10, 11], some others recommend a conservative approach through PCD (percutaneous drainage) [23, 30, 31].
The purely conservative approach with medical management (MM) only is also encouraged [32, 33, 34].
In order to overcome the differences between the therapeutic protocols, several studies have been conducted. They stratify mortality rates according to the risk variables and specifies profiles of patients' which mau not need a much aggressive management [33, 35, 36, 37, 38, 39].

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Other authors have also tried to define the therapeutic management based on the results of the CT. Nevertheless, the results of their works based on low number of patients and poor classification criteria, seems unconvincing [11, 20, 30, 40, 41].
So in the abscwnce of clear evidences, these studies are the only available guide to help clinicians in the management of EPN.
So the aim of this article is to better define the epidemiological, clinical and paraclinical – radiological – characteristics of patients suffering from EPN, to perform a systematic review of the literature, to determine the mortality rates taking into account each kind of treatment options and finally to stratify the prognostic factors described in the literature .

Methods

Search strategy and study selection.
We tried to identify every related study irrespective of the language or publication status (published, unpublished, in press, or in progress).

Data sources

We examined the Cochrane database for systematic reviews, the PROSPERO database and trial registries. MEDBASE, EMBASE and Google Scholar databases were searched by using the following words: emphysematous pyelonephritis; diabetes; kidney infection; nephrectomy; pyelonephritis; urosepsis, necrotising renal infection, and gaseous renal infection.

Data selection method

First, 3 reviewers independently identified all studies that met the inclusion criteria for evaluation.
Second, two reviewers independently extracted the data for inclusion.
Third, one reviewer correlated all data extraction.
In case of disagreement between the reviewers this was resolved by consensus.

Data extraction and analysis

We included studies reporting on three or more cases of EPN.
The main goal of this present study was to evaluate the mortality rate associated with EPN, considering the different treatment stratejies. It is noted that the three main therapeutic options are the EN, the PCD and the conservative MM. However, other therapeutics were also considered as soon as they were mentioned.

The secondary outcome was to evaluate the risk factors that were associated with death, the most common presenting symptoms, diagnostic investigations, and causative organisms.
Whenever it is possible, patients with risk factors related to mortality were compared to those with no risk factors.
Moreover, we also evaluated the mortality risk based on the different types of EPN classification.
The Wan classification divides EPN into two types.
The type I (severe) and type II (mild) [12].
The type I is defined as a parenchymal destruction - renal necrosis- with presence of gas but no fluid [12].
The type 2 is defined as the existence of parenchymal gas associated with fluid in renal parenchyma, perinephric space or collecting system [12].
Another classification called the Huang is more detailed [20], and according to it, we can define:

- class 1 presence of gas in the collecting system only
- class 2 gas in the renal parenchyma with no extension to the extrarenal space
- class 3a extension of gas or abscess to the perinephric space
- class 3b extension of gas or abscess to the pararenal space
- class 4 bilateral EPN or EPN in a solitary kidney.

The two classifications were compared.
Class I and II are considered as mild whereas class III and IV are considered as severe. That's the way we analysed them according to the studies [35, 35, 38, 42, 43].
From each study, we looked at the following variables: patient demographics, diagnostic investigations, mortality rate, presenting symptoms, culture results, laboratory findings, length of hospital stay, and treatments.
The data that were analysed were only similar results that could be pooled from the studies included.
Concerning continuous data, the test of Mantel-Haenszel chi-square was used and formulated as the mean difference with 95% CI. For dichotomous results an inverse variance was used and noticed as the odds ratio (OR) with 95% CI.
Statistical significance, was considered as P value <0.05.
To analyse heterogeneity, were used a chi-squared test on (N-1) degrees of freedom, with an α of 0.05 to indicate statistical significance, and the I^2 test, -where I^2 values of 25%, 50% and 75% corresponds to low, medium and high levels of heterogeneity-.
We also used a fixed-effect model except when there was a strong significant high heterogeneity (where $I^2 >$ 75% was recognized as a high and significant heterogeneity) between the different studies. If there was heterogeneity, we used a random-effects model.
The methodological quality of the studies included in the meta-analysis was assessed as described in the Cochrane.

Results

352 of the 463 identified studies were excluded because of the irrelevance based on the titles, and 48 others were excluded because of the irrelevance based on the abstracts (Fig.1) Full reports in 63 studies were examined, and 36 of them were included in the automatic review [19, 10, 11, 15, 16, 18, 23, 24, 30, 31, 33, 44, 45, 46, 47, 48, 49, 50, 51-58].
Most of them were published after 2008, which shows the rising awareness of EPN and the associated controversies. Although the search ncluded studies led between 1980 and 2016, all except seven of the 36 reports were published after 2000, with over half (23) published after 2007. All the studies reported patients age except for three, and all studies reported the diabetic status of the patients, while all except six reported the mortality rates associated with DM [9, 10, 11, 15, 16, 23, 31, 33, 36-42, 44, 45-47, 49,50, 51-54].
All studies except eight reported an aspect of the presenting symptoms and 23 looked at whether or not the patients were in shock, and only 16 reported death associated with shock.
29 studies reported the status of urinary tract obstruction. However only 11 of them reported death associated with urinary obstruction [9, 10, 11, 15, 16, 18, 20, 23, 24, 30, 31 33, 34, 36-49, 5154, 57, 58, 60].
All studies except eight reported laterality [10, 11, 15, 16, 18, 20, 23, 24, 30, 31 33, 34, 3649, 51-54]. 27 studies showed one or more aspects of the laboratory findings, every one of them detailed the diagnostic method used and the most common causative organism [10, 23, 31, 33-37, 38, 40, 42, 44, 47-54].

17 studies classified EPN according to the Wan classification [11, 30, 36, 37, 21, 46, 47, 58], while 19 categorized EPN according to the Huang classification [17, 33, 34, 35, 36, 38, 42, 43, 49, 16, 23]. However two of them were not included in the pooled analysis because they didn't declare which patients died according to the classification they were included in [23, 36].

Meta-analysis results

A total of 687 patients had the following characteristics:

- mean age 56.1 years,
- range (24–87) (Table 1)
- 183 Males and 504 females
- 85.7% , (589- of the patients) had DM
- 210 of 561 patients (37.5 %) had right-sided EPN
- 299 of 561 patients (53.3%) had left-sided EPN
- 53 of 561 patients (9.4%) had bilateral involvement
- In table 2, we reported the incidence of symptoms

It can be noted that pyuria is the most prevalent finding, followed by fever and rigors, shock, obstructive uropathy, haematuria and pain.
In 75.3% of the cases (266/353) leukocytosis was present, while 33.8% (87/257) had thrombocytopenia and 46.3% (206/444) had impaired renal function (acute renal failure). The organisms that were cultured are also listed in Table 2. CT was more accurate than plain radiography for detecting EPN. Indeed, CT detected 100% of cases -687 cases-, while only 56.6% -141/249-of EPN were detected using plain radiography. The number of deaths was 227 which corresponds to 33%. The mortality rates according to the different reported treatment arms are shown in table 3. Also, the OR (95% CI) are presented in Table 3 comparing differents treatments. Also, the OR (95% CI) are presented in Table 3 comparing the different treatments.
Table 4, shows the results of a subgroup analysis of the effect of the presence of risk factors on mortality.

Also in table 4, the results of a subgroup analysis based on the Huang classification are listed. The studies that were included were all case series or reports, with no randomisation or control groups. All of them reported their centers experiences regarding management of patients with EPN

Discsussion

The EPN is a rare clinical condition [5, 61, 62]. Its incidence had been steadily increasing since the deploy of CT scans. It mainly involves adults. The average age of onset for EPN is 53 years [5, 6, 7]. A predominance among females is reported by several papers, especially by Michaeli and al. [6, 8, 21], which report a sex-ratio of 1/1.8 (64% of females and 36% of males). The results of this study confirm this trend with a Female/male ratio of 2.75. Concerning the main organ affected, it seems according to some studies that the left kidney is involved in 53 to 60% of the cases vs 35% right kidney [63]. Bilateral renal involvement is rare (5 to 20%), and in those cases, the illness is particularly severe [64]. In the present meta-analysis, we noted a case of bilateral renal involvement admitted with Septic Shock and died in the immediate aftermath of a right rescue nephrectomy. The two main factors that favor EPN are diabetes – present in 85 to 96% of the cases – [8] and obstructive uropathy – in 20 to 41% of the cases [1, 9]. In the study [24] [63], patients sufferingfrom diabetes and, or obstructive uropathy were 47.6% of the total cases. However, it should be noted that EPN can occur even in the absence of these contributing factors [20]. The results obtained in the present study also reveal a predominance of PNE in diabetic subjects. The incidence rate within this category of patients is estimated at 85%. The most probable explanation to those high rates is essentially based on the physio pathological hypothesis related to an intrarenal fermentation of glucose [28]. physiopathological hypothesis related to an intrarenal fermentation of glucose [28].

Besides, Chen and al. showed that there are four main factors to the occurrence of this kind of pyelonephritis [20, 56]. It's about:

- An aerobic bacteria;
- A high intracellular glucose level;
- An ineffective tissue perfusion
- An impaired immune response.

According to Guilloneau and al., this last factor is very significant among non-diabetic patients [65].
It is to highlight that within patients without DM, glucose is thought to be substituted by urinary albumin [40].
However glucose seems to be a more favourable substrate for the gas producing organisms and thus EPN is more prevalent among patients with DM-.
The clinical signs of emphysematous pyelonephritis are not specific. The signs are generally the ones of an acute pyelonephritis (fever and rigors, pyuria and pain, with a high incidence of leukocytosis).
Other signs related to sepsis or to decompensated diabetes may be added to it.
A diagnostic latency of 7 to 21 days on average is frequent, particularly among diabetic patients, because of the insidious characteristics of the infectious symptoms [64]. In cultures, Escherichia coli, followed by Klebsiella pneumoniae then Proteus sp. were the most common reported causative organisms.
The radiological exploration represents the key to diagnosis, and makes it possible to attribute to pyelonephritis its emphysematous characteristic.
The kidney, ureter and bladder (KUB) KUB X-ray could be the first diagnostic procedure used to assess the urinary system.
Indeed, it helps to visualise the abnormal presence of aerial cavities in the kidney and to detect any opaque obstructive urinary stones. It will be noted that sensitivity of the KUB X-ray according to [5, 21, 26] would be around 30%. The renal ultrasound is very hard to read in these cases.
It can highlight dense echoes followed by reverberating echoes evoking a gas inflammation with a weak sensitivity [66, 67].
It also detects any urinary obstruction and the nature of the obstacle (gallstone, anomaly of the pyelo-urethral junction) [26, 62].
In our serie, the ultrasound was performed in 29 patients, enabling us to evoke a diagnosis in 47% of the cases.
The abdominal CT is the most common examination for the diagnosis and the follow-up of EPN [21].
Indeed, it helps to specify the type of pyelonephritis, to identify the extension of the damages and It allows also prognostic classification and therapeutic indications.
The abdominal CT has an indication in cases of fever with lumbago, among diabetic patients or in patients presenting with serious signs. It also helps to highlight the gas inflammation in the form of high negative density, to study its spread in the kidney and in the perirenal area, and to evaluate the importance of the parenchyma destruction.
Several classifications have been proposed for a prognostic purpose.
Wan and Al established in 1996 a prognostic scan classification for the EPN [12]. They were two types:

- Type 1: characterized by a parenchymal destruction (Renal necrosis) and the absence of any collection and/or with presence of gas
- Type 2: characterized by parenchymal gas associated with fluid in the renal parenchyma, perinephric space or collecting system.

In 2000, Huang and Tseng established a new CT scan classification having both a prognostic value and an impact on the therapeutic decisions [20].
Stage 1: Gas in the collecting system only;
Stage 2: Parenchymal gas only;
Stage 3A: Extension of gas into the perinephric space;
Stage 3B: Extension of gas into the pararenal space;
Stage 4: EPN in solitary kidney or bilateral disease.

The results of the present meta-analysis show that the mortality rate associated with EPN was not as high as previously reported. Indeed, the combined mortality rate was about 21%. The subgroups analysis proves that although the EPN is significantly more common among patients with DM, there was no significant difference concerning the mortality rates between patients with or without DM. (TABLE 4)

Thus in favour of the strict control and management of DM, the risk of death due to EPN becomes similar to patientsc without DM.
However, the state of shock is a major element. Indeed, it is a sign of poor prognosis. At least 37% of patients who had shock died from EPN (Table 4).
While it is rational to consider urinary tract obstruction as having a negative impact on prognosis, the results of this study reveals that the mortality rate was significantly higher in patients without obstructive uropathy. This is probably due to the aggressive management of obstruction, and thus the relief of sepsis, allowing for a better outcome. The major methods of treatment options of EPN are EN, PCD and MM. All patients were medically managed, i.e., with antibiotics, diabetic control, and fluids at presentation, before deciding on the final treatment options.
However, we noticed that:

- 37% of the patients had EN
- 14.9% had PCD
- 37.1% had MM
- 9 % had OD

When the top three treatments options were compared, it comes out that both PCD and MM have been associated with much lower mortality rates than EN.
When comparison is made between mild and severe classes, we observe a significant difference. Thus we observed more patients who died in the severe class than in the mild one, for both classifications (Wan and Huang [table 4]).
Moreover, when the severe classes of each classification were compared, there was no real difference in the death rate, which means that both classifications were accurate.
Implications on clinical practice : Considering these results, our position is that the initial medical therapy, with mainly antibiotics and fluids are needed, and adequate diabetic control remain the best solutions.
Moreover, clinicians should ought to consider either PCD of the abscess or use complete MM when the diagnosis of EPN is established.

The level of evidence provided is strengthened by collecting them and using meta-analysis of the results. Moreover, various worldwide centers reported the studies, which gives some variability to the data, thus allowing for the generalisation of the final conclusions. Nevertheless, the present review is marked by an impartial work, systematically and methodically led by Cochrane standards.

Conclusion

What is shown in the results of this systematic review and meta-analysis is that EPN has an approximately 21% overall mortality rate.
The PCD and MM procedures are associated with significantly higher survival rates than those of the EN procedures.
Thus, EN should only be considered if there is evidence of an absence of improvement -in the patient's condition- despite other appropriate procedures.
Immediate management of diabetes as well as aggressive treatment of septicemia significantly improves survival.
Computed tomography remain the most appropriate diagnostic test.
Finally, it should be noted that severe EPN is often associated with a high mortality rate.
Thus more aggressive treatment is therefore recommended.

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Table 1 The studies included and patient demographics.

Ref.	Period	M:F	Mean (range) Age, years	R:L:bilat:graft
[9]	NM	8:3	56.3	NM
[10]	1980–95	5:15	55	7:12:1
[11]	1991–99	1:20	61 (11.1)	9:11:1
[16]	2003–2005	7:13	54.4 (20.6)	10:06:2
[17]	2004-2011	5:7	64.3 (13.7)	5 :7 :0
[20]	1989–97	7:41	60	12:32:4
[23]	2000–2010	8:25	51 (10.9)	12:15:3
[24]	1987–2004	6:15	54.6	6:14:1
[30]	1984–95	7:18	60.6	13:12
[31]	1993–2004	3:23	58.7 (12.7)	13:11:2
[33]	1995–2009	11:12	62.8 (17.1)	8:13:1:1
[34]	2008–2011	4:4	49.63 (8.99)	?:?:4
[35]	2004–2008	6:33	57 (7.2)	6:28:4
[36]	2005–2010	1:17	52.4	NM
[37]	1986–93	5:33	54.7	?:?:2
[39]	2001–2007	3:13	61.2 (11.5)	6:9:1
[38]	2001–2007	3:16	43.6 (8.9)	3:11:5
[40]	2000–2009	7:17	61.8	11:11:2
[41]	1986–96	7:21	61.6	13:14:1
[42]	2001–2007	22:19	55 (7.3)	19:13:8
[43]	2005–2009	10:18	NM	NM
[44]	1996–2004	1:6	44.5	2:5
[15]	1980–85	3:10	53	7:5:1
[45]	NM	2:3	53 (4.77)	NM
[46]	2006–2010	3:10	NM	5:4:4
[47]	1992–2002	1:9	61.2	NM
[48]	1987–2009	10:20	58.5	9:20:1
[49]	NM	2:3	51 (16.39)	3:2
[50]	NM	4:4	NM	10:06:2
[51]	1986–91	2:2	62 (11.34)	NM
[52]	NM	1:3	51.25 (10.21)	2:2
[53]	1998–99	1:5	63.8 (13.63)	3:1
[54]	1986–2004	5:12		3:2
		52		7:8:
				2

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Table 2 Symptoms and the organisms cultured

Symptoms	n/total n (%)
Pyuria	161/206 (78.2)
Fevers and rigors	375/482 (77.8)
Pain	332/441 (74.3)
Haematuria	82/207 (41.5)
Shock	119/494 (24.0)
Obstructive uropathy	226/631 (35.8)
Organism cultured	
Blood culture	
Escherichia coli	225 /410 (54.8)
Klebsiella pneumoniae	27/216 (12.5)
Proteus sp.	3/77 (3.8)
Urine culture	
Escherichia coli	370/603 (61.3)
Klebsiella pneumoniae	82/424 (19.3)
Pseudomonas sp.	6/102 (5.8)
Proteus	10/147 (6.8)
Pus culture	
Escherichia coli	115/208 (55.2)
Klebsiella pneumoniae	26/142 (18.3)
Negative cultures	
Blood	99/339 (29.2)
Urine	127/366 (34.7)

Table 3 Treatments and associated mortality rates, with the risk comparisons of treatments.

Treatment	No. of deaths/total (%)	
EN	74/193 (37.2)	
PCD	56/353 (14.9)	
MM	88/223 (37.1)	
OD	7/77 (9.0)	
	Comparison, OR (95% CI)	P
EN vs. PCD	3.53 [2.2929 ; 5.4993]	< 0.001
PCD vs. MM	0.28 [0.1915 ; 0.436]	< 0.001
EN vs. MM	0.95 [0.6298 ; 1.4438]	0 0.84

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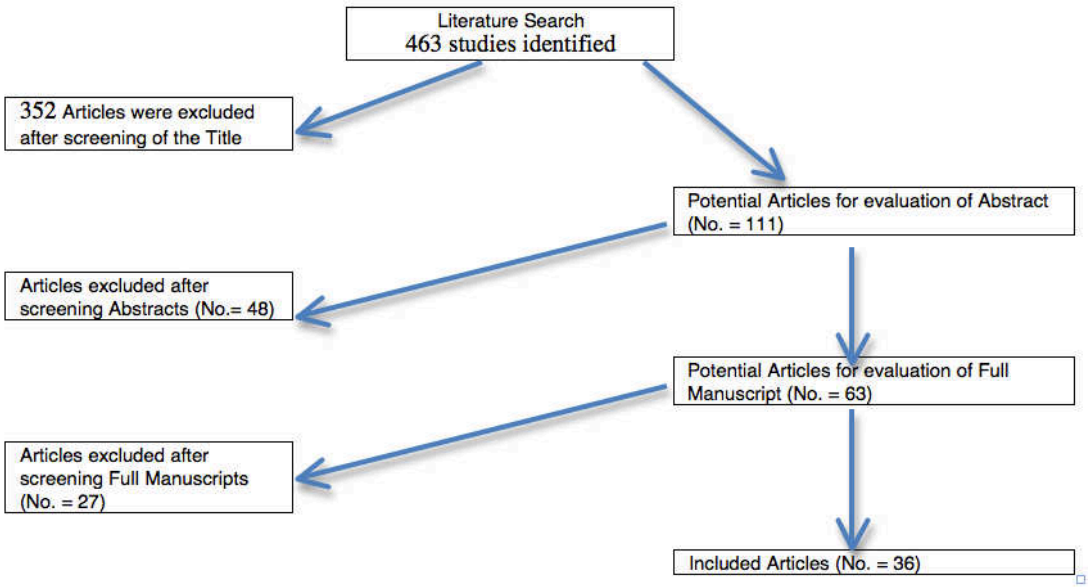
Table 4 Risk factors and CT classifications with associated mortality rates.

Risk factors	Deaths/total reported	**Risque attribuable (RA)**	OR (95% CI)
DM vs. no DM	83/ 417 vs. 17/ 61	-7.97	0.64 (0.35–1.18)
Shock vs. no shock	47/ 126 vs. 17/ 233	30.00	7.56 (4.32–13.23)
Obstruction vs. no obstruction	16/53 vs. 35/97	-5.89	0.77 (0.38–1.56)
Huang Class I + II vs.III+ IV	9/147 vs. 43/137	-25.27	0.14 (0.07–0.28)

Fig. 1 **The flowchart of the articles selected.**



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