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TROPICAL MEDICINE IN THE MEDITERRANEAN REGION (F BRUSCHI, SECTION EDITOR)

Cystic Echinococcosis in the Mediterranean

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Abstract
Purpose of Review Cystic echinococcosis (CE), a zoonotic disease caused by *Echinococcus granulosus* sensu lato, is endemic in the Mediterranean, where pastoral activity is widespread, as the life cycle of this helminth involves sheep, as well as other livestock, as intermediate hosts. We review recent studies on CE from Mediterranean countries.
Recent Findings Reliable data on CE, from human and animal epidemiology to treatment, remain fragmented and insufficient to gauge the magnitude of the problem beyond local communities. The lack of major advances leaves clinicians without an evidence base on which to make sound clinical decisions.
Summary Despite a wealth of publications on the subject, CE remains a neglected disease in the Mediterranean as well. Hope is seen in the establishment of a European Registry for Cystic Echinococcosis, but implementation and maintenance of such an important tool will require hard work, political commitment and resources, monetary, and otherwise.

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Introduction

Cystic echinococcosis (CE) and alveolar echinococcosis (AE) are two zoonotic diseases caused by tapeworms belonging to the *Echinococcus* genus. CE is a cosmopolitan zoonosis present in countries across all continents excluding Antarctica, whereas AE is limited to the northern hemisphere [1]. Human CE affects an estimated 1.2 million people worldwide, with 1 to 3 million disability-adjusted life years (DALYs) lost globally every year, although these figures are likely to be underestimated [1–3]. *Echinococcus granulosus* sensu lato (sl), the causal agent of CE, develops its cycle between dogs and other canids (definitive hosts) and livestock, especially sheep (intermediate hosts), with humans as an accidental intermediate host. In humans, the parasite develops in its metacestode stage, forming cysts in organs and tissues, mainly in the liver. CE is mostly endemic in rural areas where sheep (and other livestock) raising is practiced, such as central Asia and China, South America, and Mediterranean countries [1]. In 2012, a joint FAO/World Health Organization (WHO) expert group classified *E. granulosus* second among the top 8 food-borne parasites of global public health importance. Here, we review studies on human and animal CE carried out in the Mediterranean countries in the last 3 years.

Materials and Methods

We performed a PubMed (MEDLINE) search for articles on CE published in English and French between 1 January 2014 and 30 May 2017 reporting data from any of the following

countries in the Mediterranean region. The following search string was applied: (Cystic Echinococcosis OR *E. granulosus*) AND (Mediterranean OR Italy OR France OR Spain OR Algeria OR Morocco OR Bosnia Herzegovina OR Slovenia OR Egypt OR Syria OR Montenegro OR Albania OR Greece OR Turkey OR Cyprus OR Lebanon OR Israel OR Palestine OR Libya OR Malta OR Tunisia). We included original papers on CE epidemiology in humans, CE epidemiology in animals, molecular biology, and clinical management. Review articles, case reports, case series considering less than 15 patients, and studies carried out in countries outside the Mediterranean region were excluded (Fig. 1). Ninety records matched our inclusion criteria.

Risk Factors for CE

Among the articles who dealt with risk factors for infection with *E. granulosus*, two reported data from public health surveys in Morocco [4, 5]; one assessed the level of knowledge about CE and the prevalence of risk factors in an endemic, rural area of the country and found that the local population had a scarce knowledge of the disease and of its risk factors and that 67% of respondents fed dogs ruminant offal deemed unfit for human consumption [4]. A similar lack of awareness on CE was found in the other study examining the social factors influencing the transmission of the disease including the role of markets and abattoirs [5]. The faulty management of abattoirs can favor transmission as state regulations, perceived as economically unfavorable, are not followed [5].

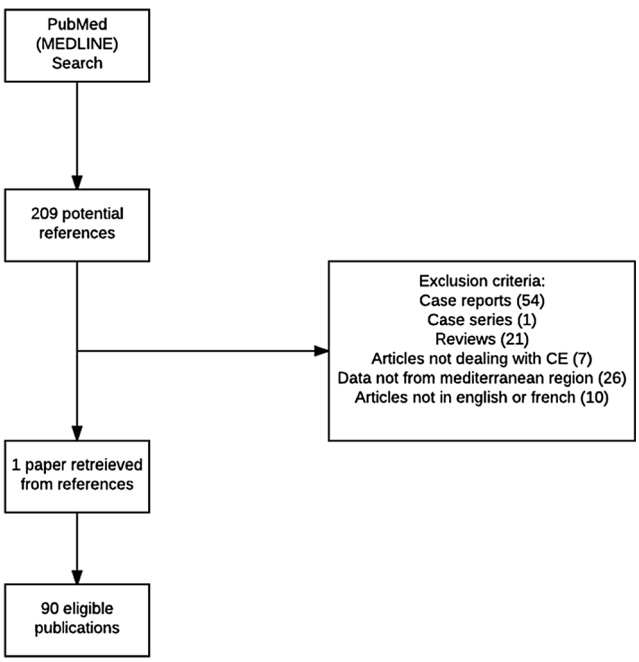

Fig. 1 Flow diagram detailing the publication inclusion process

Dogs were seen gathering around slaughterhouses to feed on the remnants of the carcasses [5]. A similar situation emerged from a survey of abattoirs conducted in Algeria, where 42% of the slaughterhouses allow free access of dogs to fresh offal [6]. However, a study conducted in Tunisia on *E. granulosus* eggs present in soil found no difference between the contamination rates in sites close to slaughterhouses and far from them [7]. The authors suggested that behavior of dogs may be more important than the location of the sources of infection [7]. A study of an educational intervention on neglected zoonoses targeting the general population in Morocco [8] showed that although the intervention increased the awareness of the disease in target communities, target interventions for CE still need the surveillance on the pathogen in intermediate and definitive hosts to be effective [9]. A study from Turkey on the prevalence of risk factors among family members of breeders tried to correlate the presence of risk factors with serological results [10]. They found a positive serology for CE in 6.9% of the 1113 individuals screened, with a statistically significant association between the presence of CE and two age groups (30–39 and > 60) and with the lack of routine veterinary supervision on animal health. Contact with dogs or ownership of cattle or sheep was not associated with a positive serology [10]. The significance of these findings should be considered with caution, given the limits of seroprevalence studies (see below). Moreover, these findings do not concur with those of another study carried out in Morocco, which found that the ownership of dogs was significantly associated with the presence of CE cysts in patients screened by ultrasound. This study also found a borderline association with the ownership of cattle [11••].

Burden of Human CE

We found 30 articles on the epidemiology or burden of human CE. Among seven articles from Spain, one compared a cohort of 16 non-Spanish patients with 534 Spanish patients and found a higher incidence in the latter group [12]. The incidences were calculated taking the total Spanish and migrant population of Salamanca as references. The authors explain this difference with the fact that in Spain, immigrants tend to seek medical advice less frequently than natives [12]. Another study found the mortality of CE to be 3.1 cases per 100.000 inhabitants [13], while a paper on a cohort of 76 patients in a single center did not find any case of CE-related mortality [14]. Several studies in our review used hospital discharge records (HDRs) as a source of data to study CE epidemiology. HDRs provide information on the cause of the hospitalization defined according to the International Disease Classification. In Spain, a study using the national HDR database and a study using HDRs in the Castilla-Leon

region showed a reduction of the number of cases of CE in recent years, as did a single-center study from Salamanca [15–17]. These studies noted that data from the official notification system showed fewer cases than those recorded in the studies themselves [15, 16]. Conversely, three regions in Spain showed an increase in the number of reported cases over a 16-year time frame [15]. The seventh study from Spain considered the economic impact of CE on a single province [18]. Estimates included in this study considered losses due to decreased production of meat and milk on the animal side, while the costs derived from healthcare expenses and the loss due to decreased productivity were considered for human estimates. Total estimated losses ranged from €61,864 to €360,466, with human-associated costs accounting for 57 to 97% of the total expenses depending on the simulated scenario [18].

Among six papers published in Italy, one investigated the cost of surgery for abdominal CE in a single center and found the mean cost of a hospitalization for an abdominal surgical intervention to be €11,033 [19]. Another article from Italy on neglected tropical diseases in non-Italian patients showed that CE was more frequent in immigrants than in Italian patients [20]. A study of HDRs in Italy showed a mean number of 1379 hospitalizations per year, with most records being registered in southern and central Italy. Data from this study also showed that an official surveillance system is needed in Italy, as currently no notification-based system is active [21]. This study also reported that a high number of hospitalizations to treat patients with CE were carried out at day hospital for medical treatment, which represents, to say the least, a waste in resources as medical therapy does not need supervision in the hospital [22]. In a study using HDRs in France, the overall number of cases was inferior to those of Italy and Spain [23]. While there seems to exist a reduction in the number of cases over time, the authors point out the persistence of autochthonous transmission, with possible high levels in Corsica [23]. Given the high number of immigrants coming to France from countries in the Maghreb where CE is endemic, the reported average 0.42/100.000 incidence rate is most likely underestimated. Moreover, HDR only accounts for CE patients admitted to hospitals to be treated for CE, with asymptomatic patients and those managed in an outpatient setting escaping this analysis [22, 24]. A study analyzing hospital records from a single center was also published in Israel, with the majority of cases occurring in nomads coming from the southern part of the country [25]. Other papers analyzed the epidemiological characteristics of patients seen in single centers in Turkey [26–30]. These studies showed the presence of a high number of patients, but they did all suffer the limitations of retrospective, single-center studies. A systematic analysis of national data from Turkey would greatly help in clarifying the disease burden in the country.

Several studies in our review focused on the seroprevalence of CE [10, 31–33].

Unfortunately, serology tells nothing about the presence of CE as serological tests present a high variability in results due to the interaction between test sensitivities and specificities and the fact that the performance of serological tests as tools for screening depends on the underlying prevalence of disease [34].

It is quite depressing that almost 40 years from the publication of the seminal work by Macpherson and colleagues [35], this message has not come across to the scientific community.

Ultrasound is the only tool we have that can give us information about presence, location, stage size of cysts, and be portable at the same time. This is why over the years, screening programs have been increasingly carried out to assess CE prevalence in selected populations.

A recent ultrasound study assessed the prevalence of CE in two endemic provinces in Morocco using portable ultrasound [11••]. Such surveys can provide a more precise estimate of the infection prevalence compared to hospital-based records and be the occasion to inform local health authorities and population on the existence of CE and its health implication. In this study, most CE patients were asymptomatic and most cysts were inactive. However, the study also demonstrated an ongoing transmission of CE in the studied areas, as shown by a prevalence of 1.9% found by Chebli and colleagues, compared to 1.1% reported in an earlier study [11••, 36].

Besides ultrasound studies, the many gaps in the official systems of data collection have prompted the initiation of CE registries. The first such registry implemented was the Italian Registry of Cystic Echinococcosis (RIEC), an Italian national registry that was launched in 2012 and then expanded into a European Registry for Cystic Echinococcosis (ERCE) [37, 38••].

ERCE was launched in 2014 in the context of the HERACLES project (www.heracles.fp7.eu), an FP7-founded project that is still running at the time of this writing and that, among other things, addresses the epidemiology of CE on an international scale. Interestingly, data from ERCE published in 2016 showed that the cases present in the registry outnumbered cases reported through institutional channels already put in place by the European Centers for Disease control (ECDC) [37]. This confirms that the epidemiological figures of CE in Europe and in the Mediterranean region are vastly underestimated.

CE in Animals

Classical epidemiological studies on prevalence of CE in intermediate hosts are based on necropsy of slaughtered animals in abattoirs. One study carried out in Sardinia on animals, tested after control measures were dropped, saw a decrease in the number of cysts and an increase in cyst fertility [39].

The authors also proposed a morphological classification of cysts to recognize fertile cysts and monitor the level of parasite pressure in a control perspective [39]. Other studies have also assessed CE prevalence in other hosts and countries. Results from recent surveys are summarized in Table 1 [39–42]. One article concerning the prevalence of infection by intestinal parasites in dogs examined in Crete found that shepherd dogs harbored taeniid eggs at a higher prevalence than household dogs [44]. However, no molecular methodology has been employed to identify the exact taeniid species of the eggs.

Ultrasound of cysts in intermediate hosts has also been proposed. Ultrasound in sheep had 83% sensitivity and 100% specificity in one study [45] and 88.7% sensitivity and 100% specificity in a second study [46]. Ultrasound was compared with necropsy examination and performed better than in previous reports. Dore and colleagues suggest that the integration of ultrasound in programs trying to detect CE in sheep would allow for the culling of infected sheep before these reach the abattoirs, thus diminishing the possibility of disease transmission to canids [45]. However, this procedure appears to be difficult to implement in endemic areas. A Turkish team studied a small cohort of animals in which the total antioxidant capability (TAC) of lambs and sheep with CE was reduced compared to that of healthy subjects and suggested using ultrasound with the measurement of TAC for CE diagnosis. This seems difficult to reproduce on larger cohorts in endemic areas [47].

Another study looked at *Rattus norvegicus* as a potential intermediate host for CE [48], suggesting that rats can harbor fertile CE cysts and thus may contribute to the continuation of the parasite life cycle.

Geospatial tools are another way to study prevalence in animals [49, 50]. The authors of these papers use data from systems tracking the presence of zoonotic infections in cattle to spot foci of CE transmission. One survey using geospatial analysis tools assessed the prevalence of infected animals in dairy farms in northeastern Italy and found that, despite the fact that the region is considered hypoendemic, three clusters of transmission were present [49]. A similar approach was also used in Sardinia [50].

Genetic Diversity

Molecular studies can supplement classical epidemiological data on CE epidemiology in the Mediterranean. Mitochondrial markers can differentiate *E. granulosus* into nine genotypes: *E. granulosus* sensu stricto (*ss*) (G1–G3), *Echinococcus equinus* or "horse strain" (G4), *Echinococcus ortleppi* or "cattle strain" (G5), and *Echinococcus canadiensis* (G6–8 and G10), further divided into a "camel strain" (G6), a "pig strain" (G7), and two "cervid strains" (G8 and G10) [51••]. We found 18 studies on the genetic diversity of *E. granulosus* using samples originating from countries in the Mediterranean region and coming from several hosts. Our findings are summarized in Table 2.

The G1 genotype is the most frequently isolated in the region and is responsible for 88% of the *E. granulosus* infections worldwide [51••]. A study considering only G1 samples from different hosts [51••] has shown that no host-specific substructure exists in the G1 genotype, as samples from different hosts were genetically close to each other. As the authors state, a high genetic diversity suggests a demographic expansion of the studied population and could constitute the background for the association of the G1 genotype with new species if the diffusion of the genotype in Europe widens; such diversity could also pose the basis for the development of drug resistance [51••].

Another study on phylogeny of *E. granulosus* considered both the classical mitochondrial markers and two nuclear markers [58••]. The authors analyzed samples of *E. granulosus* ss originating from Mediterranean and other regions and concluded that when also nuclear markers are taken into account, the G1 and G3 genotypes should be treated as different species. Their analysis of data from the sole mitochondrial markers also suggests that the G2 genotype should no longer be considered a distinct genotype. These findings need confirmation by further work [58••].

Diagnostic Serology

The diagnosis and management of CE relies on ultrasound with serology as a complementary tool. Several factors, including the cyst size, stage, and number, influence serological results [62]. Research efforts have been trying to improve this situation by testing the role of new antigens in serologic tests for CE [33]. Current serological tests are based mainly on crude hydatid cyst fluid (HCF) or purified/enriched antigens obtained from cyst fluid [63]. Overall, the diagnostic performances and reproducibility of results are not unsatisfactory due to the lack of standardized antigen preparations and to the poor sensitivity and specificity of the antigens [63]. Among the recent studies included in this review, a new assay using antigen 5 was described, with encouraging results [64, 65]. Antibody tests based on P-29 and 2B2t antigens were proposed as useful for the serological follow-up of patients after surgery; however, they became negative after surgery in most patients, but were not sensitive enough to detect recurrences [66, 67]. Recently, the performances of rapid diagnostic tests (RDTs) were also evaluated [68, 69•, 70].

Imaging

A single study from Turkey used diffusion-weighted MRI to differentiate CE1, CE2, and CE3 cysts from CE4 and CE5

Table 1 Summary of data presented in articles concerning epidemiological surveys of cysts in intermediate hosts

Article	Sample origin	Host species (*n*)	Animal (*n*)	*N* infected (%)	Fertility rate (%)
Conchedda et al. [39]	Sardinia (1st survey)	Sheep	1375	1029 (74.84%)	7.9%
	Sardinia (2nd survey)	Sheep	1414	916 (64.78%)	10%
Uhmang et al. [40]	Corsica	Pig	2527	149 (5.9%)	30%
		Wild boar	101	4 (4%)	25%
		Cattle	2431	0 (0%)	(0%)
		Sheep	5970	0 (0%)	(0%)
Abbas [41]	Egypt	Water buffaloes	120	5 (5.2%)	14.8%
Chaligiannis et al. [42]	Greece	Sheep	898	271 (30.2%)	64.5%
		Goats	483	38 (7.86%)	3.2%
		Buffaloes	38	16 (42%)	7.9%
		Wild boars	273	3 (1.1%)	0%
		Deer	15	(0) 0%	0%
Lahmar et al. [43]	Tunisia	Donkey	2010	173 (8.48%)	4.77%

cysts and found a sensitivity of 75.9–87% and a specificity of 86.8–89.5% depending on the MRI settings [71]. However, ultrasound is best at staging CE in the liver [72] and is far less expensive, and far more repeatable than MRI [73, 74].

Biological Markers

Research efforts have been aimed at discovering new markers of biological activity for CE cysts, as summarized in [75], as currently available serological markers are unreliable for diagnosis and follow-up. After one study found that a Th2 immune response is dominant in patients with active cysts [67], an Italian group recently suggested that the production of IL-4 by white blood cells stimulated with an immunodominant antigen of *E. granulosus* could correlate with cyst activity, but the authors also admitted that a larger study was needed to provide evidence [76]. In another study, T regulatory cells also seem to play a predominant role in ovine CE [77]. A study considering a small group of mice infected with CE and breast cancer cells found that a decrease in Th1 immunity led to an increase in the frequency of cancer metastasis, but this association has never been described in humans [78]. Serum sHLA-G levels were also found to correlate with CE activity, although this molecule would not be a suitable marker in individual patients [79]. Recently, the existence of parasitic exosomes of *E. granulosus* was also confirmed by a Spanish group [80••]. The study of exosomal proteins could provide new markers for the detection of CE in humans and animals. A study by a team from Algeria also reported that proteome variations could be observed in cysts with different localizations [81], although only three patients were considered in this study.

Studies on Clinical Management

The clinical management of CE is complex [82]. Currently, treatment options include percutaneous treatments, surgery, the use of benzimidazoles, and a watch-and-wait approach. The approach to clinical decision-making should be guided by ultrasound-based staging [83].

Drug Therapy

Benzimidazoles are currently the only available drug class to treat this disease, but they are only parasitostatic. Over the years, this has led to the search for more efficacious molecules or formulations [82, 84]. Recently, a new albendazole salt has been patented [85, 86]. It has been suggested that the laminated layer of echinococcal cyst could trigger the induction of arginase and therefore NO production to modulate the response from the host macrophages [87]; building on this finding, a group from Algeria published three papers on the anthelmintic effects of 6-gingerol, *Punica gratum*, and *Allium sativum* extracts, to investigate their influence on NO production, but, even if confirmed, clinical applications are still very distant [88–90].

Percutaneous Treatments

Studies on percutaneous treatments (PTs) have recently been published by Turkish teams. These studies have been testing catheter-based techniques or variations of the puncture, aspiration, injection, re-aspiration (PAIR) technique and showed that the techniques are safe if carried out with the proper

Table 2 Summary of studies exploring the genetic diversity of *E. granulosus* in the Mediterranean area

Article	Sample origin	Host species	Genotype
Lahmar et al. [43]	Tunisia	Donkey	G4 and G1
Di Paolo et al. [52]	Italy	Wild boar	G3
Umhang et al. [40]	France	Pigs	G6–G7
		Cattle	G6–G7
		Wild boars	G6–G7
Yoshra et al. [53][a]	Egypt	Camels	G6
		Pigs	G6, G7
		Humans	G6, G7, G1
Chaligiannis et al. [42]	Greece	Sheep	*E. granulosus ss*
		Goats	*E. granulosus ss*
		Buffaloes	*E. granulosus ss*
		Wild boars	*E. granulosus ss*
Kinkar et al. [51••][a]	Albania	Sheep	G1
	Finland (patient from Algeria)	Humans	G1
	Greece	Humans	G1
	Italy	Cattle, sheep	G1
	Spain	Sheep, human, wild boar, pig, goat	G1
	Turkey	Cattle, sheep	G1
Simsek et al. [54]	Turchia	Donkeys	G4
Gori et al. [55]	Italy	Wolf	*E. granulosus ss*
Poglayen et al. [56]	Italy	Wolf	*E. granulosus ss*
Abbas [41]	Egypt	Buffaloes	G1
[57]	Greece	Sheep	*E. granulosus ss*
		Goats	*E. granulosus ss*
		Cattle	*E. granulosus ss*
Kinkar et al. [58••][a]	Albania	Sheep	G1
	Finalnd (patient from Algeria)	Humans	G1
	Tunisia	Sheep	G1, G3
	France	Cattle, sheep	G3
	Spain	Sheep	G1, G3
	Turkey	Cattle, sheep	G1, G3, G4
Boufana et al. [59][a]	Libya	Dog	–
	Tunisia	Dog	–
	Palestine	Dog	–
Boufana et al. [60][a]	Tunisia	Wild boars	*E. granulosus ss*
		Camels	G1, G6
		Cattle	G1
		Goats	G1
		Donkey	G1, G4
		Sheep	G1
		Dogs	–
		Jackals	–
Bakal et al. [54]	Turkey	Human	*E. granulosus ss*
Scala et al. [50]	Italy	Cattle	G1
Zait et al. [61]	Algeria	Camels	G1, G6
		Cattle	G1
		Goats	G1
		Sheep	G1
		Human	G1, G3, G6

[a] Include also samples not coming from the Mediterranean region

infrastructure and expertise [91, 92]. Among the studies found in our review, one tested a variation of the PAIR technique in which the re-aspiration step was not performed (PAI) on 25 patients [93]. This, in our opinion, is dangerous as permanence of scolecidal agent in the cavity increases the risk of chemical cholangitis, a dreaded complication of this technique. Further, the authors claim that they treated also CE4 cysts, which are inactive and solid, and their follow-up was too short to conclusively evaluate the effectiveness of the procedure (12 months).

Another study explored PAIR in an outpatient setting and found that this technique can indeed be used without hospitalization. This is potentially interesting for low-resource settings, but given that only 33 cysts were treated in this way, larger studies are needed to confirm its safety [94]. A study proposed the Ormeci technique, an

alternative to PAIR where the patient is treated in an outpatient setting with the scolicidal agent being left in situ with the addition of polidocanol to prevent biliary fistulae, and does not receive benzimidazole derivatives to prevent relapses. This proposal appears debatable, for the same reasons outlined above and given that the author himself admits that treatment for recurrences would be administered on an "as-needed" basis [95].

Interestingly, some of these studies used PTs on CE3b and CE2 cysts, which are currently not indicated for these two cyst types [93, 96]. However, they are retrospective and do not compare PTs with surgery. Prospective trials are needed to assess the efficacy of PTs in the treatment of CE3b [96] and CE2 cysts. A watch-and-wait approach has been used for CE3b cysts in selected conditions [97], although once again the study was retrospective.

A study from a single center stated that in complicated cysts, surgery is superior to PTs [98]; one paper tested ERCP in patients with biliary fistulae and found this method to be safe and effective [99]. These indications are well known [83].

A study from Egypt found that gamma radiation induced the apoptosis of *E. granulosus* metacestodes, but radiation therapy has provided unsatisfactory results in other studies [100, 101].

Lastly, a team of surgeons from Morocco proposed a systematic approach for the management of cystobiliary fistulae in the treatment of CE cysts, which reduced the rate of complications and the duration of hospital stay, leading to a reduction in costs [102]. However, this strategy needs to be tested in larger, multicenter studies [102].

Conclusions

Many studies have been published on CE in the Mediterranean basin in the last 3 years. Unfortunately, the vast majority does not contribute any significant advancement in the areas surveyed by our review. Some hope can be found in initiatives aiming to provide the missing data on cyst evolution in a systematic and prospective way in surveyed countries, like ERCE, but the obstacles to continuing data collection are daunting, and coordinated efforts will be needed to keep the project going in the future. As long as there is a lack of evidence base and prospective, randomized (and costly) trials, the only advances in this area can come from incremental improvement obtained in referral centers with a large enough caseload.

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Compliance with Ethical Standards

Conflict of Interest Raffaella Lissandrin, Tommaso Manciulli, Mara Mariconti, and Ambra Vola declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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