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Progress towards international adoption of the World Health Organization ultrasound classification of cystic echinococcosis

E. Mirabile[a,1], N. Solomon[a,c,1], P.J. Fields[a,b,c,1], C.N.L. Macpherson[a,b,c,*]

[a] School of Medicine, St. George's University, Grenada
[b] School of Veterinary Medicine, St. George's University, Grenada
[c] Windward Islands Research and Education Foundation, Grenada

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ABSTRACT

Cystic echinococcosis (CE) is a global parasitic zoonosis for which ultrasound (US) is the gold standard modality for diagnosis. In 2003, the WHO published a standardized US classification of CE, on which WHO treatment guidelines are based. In 2014, global adoption of the classification was questioned by a publication which indicated that, between 2004 and 2014, only half of studies utilizing a classification used the WHO classification. More recent studies have demonstrated that the WHO classification best reflects the natural history of CE, and is used with high reliability by experts in the field; despite these attributes, the classification's impact is ultimately limited by the extent of its adoption. A PubMed search using the terms "Echinococcus granulosus ultrasound," "Echinococcus granulosus classification," "cystic echinococcosis ultrasound," and "cystic echinococcosus classification" revealed publications on human CE utilizing a US classification. Classification(s) used, year of publication, and the country of the first author's institution were recorded. From 2004 to 2010, the WHO classification was used in 50% or fewer of included publications for 6 of the 7 years. After 2011, it appeared in a low of 75% (2013) to a high of 96% (2017) of included publications. Of all included studies published from 2004 to 2017, the WHO classification was referenced in 18% (3 of 17) from Africa, 64% (32 of 50) from Asia, 79% (89 of 113) from Europe, 89% (8 of 9) from North America, and 100% (9 of 9) from South America. Findings suggest that the WHO classification has been progressively taking preference to other classifications, with rate of adoption depending on continent of origin of the research. Residual use of the classification developed by Dr. Hassen Gharbi of Tunisia in 1982, used widely prior to development of the WHO classification (which reversed two stages in Gharbi's classification in order to more closely reflect the natural history of CE) suggests that adoption of a new classification takes time and varies regionally.

1. Introduction

Cystic echinococcosis (CE) is a chronic, complex zoonotic disease resulting from infection with the cestode *Echinococcus granulosus* (Symeonidis et al., 2013; Thompson and McManus, 2001). Infection occurs when humans accidentally ingest *E. granulosus* eggs, which hatch into oncospheres and enter the portal circulation via the gastrointestinal tract. Oncospheres develop into cysts within the organs and body tissues, particularly in the liver and lungs (Symeonidis et al., 2013; Thompson and McManus, 2001; Kern, 2003). In regions where CE is endemic, 60–75% of patients are asymptomatic (Belard et al., 2015); but the disease can be complicated if cysts become secondarily infected, rupture, or impinge on surrounding structures (Pawłowski et al., 2001).

There is currently no standard, highly sensitive and specific serological test for CE antibody detection (Pawłowski et al., 2001). Factors like the high rate of false-negatives, high expense of materials and reagents, long processing time, invasive nature of the tests, and ease of test contamination outside of the laboratory make serology not impossible, but difficult to use in field settings (Pawłowski et al., 2001; Macpherson and Milner, 2003; Macpherson et al., 1987). A 1987 study on patients with CE in Turkana, Kenya, found ultrasound (US) data superior to serological data, which identified only 50% of patients with cysts and could not provide information regarding cyst location, size, or condition (Macpherson et al., 1987). Serology also cannot be used to monitor changes in cysts.

US has been used to detect a variety of pathologies, including parasitic infections, since the 1970s, with the use of portable US

* Corresponding author at: St. George's University School of Medicine, P.O. Box 7, St. George, Grenada.
E-mail addresses: emirabil@sgu.edu (E. Mirabile), nsolomon@sgu.edu (N. Solomon), pfields@sgu.edu (P.J. Fields), cmacpherson@sgu.edu (C.N.L. Macpherson).
[1] St. George's University, P.O. Box 7, St. George, Grenada.

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scanners in rural communities starting in 1980s. The advent of portable US screening has allowed for more effective mass surveillance and evaluation of CE prevalence among asymptomatic human populations (Macpherson et al., 1987; Macpherson, 1992; Solomon et al., 2017a). With high sensitivity (88–98%) and specificity (95–100%) for CE, US can be used to quickly and easily visualize clear pathognomonic signs of the disease (Pawłowski et al., 2001; Macpherson et al., 1987; WHO-IWGE, 2003), and because is painless and non-invasive US is accepted by populations in field settings.

The complexity of CE led to the development of numerous classifications, the first of which was a US classification developed by Gharbi in 1981, which was followed by approximately 30 other classifications for clinical or epidemiological natural history purposes (WHO-IWGE, 2003). This confusing situation led in 1994 to the World Health Organization Informal Working Group on Echinococcosis (WHO-IWGE) proposing the development of a WHO standardized US classification which was agreed upon in 2003 (WHO-IWGE, 2003) and updated in 2010 (Brunetti et al., 2010). Since then, studies on the WHO classification have revealed that it both reflects disease natural history, and can be used by experts in US and CE to reliably classify cysts (Solomon et al., 2017b, c), findings which support and promote adoption of the classification by clinicians and researchers working in the field.

A 2014 study evaluating the acceptance of the WHO classification reviewed papers published from January 1, 2004 through April 30, 2014, and found that, of those utilizing a US classification, 48.8% utilized the WHO-IWGE classification, 47.9% utilized the Gharbi classification, and 3.3% utilizing other classifications altogether (Tamarozzi et al., 2014).

Because the WHO classification has been demonstrated to more accurately reflect disease natural history than other classifications and treatment guidelines for CE are based on the WHO system, appropriate and effective treatment relies on the proper application of the WHO classification by clinicians (Brunetti et al., 2010). This study builds upon the previous study evaluating international classification use in order to determine whether WHO classification usage has increased since publication of the prior study, and to identify factors which may be preventing its universal adoption around the world.

2. Materials and methods

This study represents a combined secondary evaluation of a data set from a previous study (Tamarozzi et al., 2014), with the addition of papers published after the previous study's publication, through November 30, 2017. Publications utilizing a US classification to stage CE were collected in order to analyze classification usage over time and on different continents. A PubMed (MEDLINE) search was conducted, using the search terms "echinococcus granulosus ultrasound," "echinococcus granulosus classification," "cystic echinococcosis ultrasound," and "cystic echinococcosus classification" in order to identify studies utilizing US and a US classification. Publications focusing on *E. granulosus* infection and utilizing a US classification were included in the data set, as long as use of a classification and classification type could be identified within an available abstract or full text (regardless of language). Studies on other *Echinococcus* species and animal studies were excluded. Classification(s) used, year of publication, and country of the institution with which the first author was affiliated were recorded.

3. Results

A PubMed search resulted in a data set composed of 198 articles, published between January 1, 2004 and November 30, 2017. Evaluation of these 198 articles revealed use of the WHO classification, the Gharbi classification, a combination of these, and others (Table 1).

The number of articles published each year since 2004 was then tabulated (Table 2), followed by an assessment of where the articles originated based on country of first authorship (Table 3).

Table 1
Utilization of the Gharbi classification, WHO classification, a combination, and others.

Publications by Classification(s) Utilized		
Classification	Frequency	Percent
Gharbi	51	25.8
WHO	130	65.7
Gharbi & WHO	11	5.6
Gharbi & Other	1	0.5
Other	5	2.5
Total	198	100.0

Table 2
US classification utilization by year.

Publications by Year		
Year	Frequency	Percent
2004	2	1.0
2005	9	4.5
2006	4	2.0
2007	11	5.6
2008	15	7.6
2009	7	3.5
2010	15	7.6
2011	16	8.1
2012	28	14.1
2013	16	8.1
2014	19	9.6
2015	15	7.6
2016	18	9.1
2017	23	11.6
Total	198	100.0

To demonstrate classification use over time, the percentage of papers utilizing each classification (or combinations) each year were graphed (Fig. 1).

This data was further evaluated to show classification usage by location (specifically, by continent) since the WHO classification was published (Fig. 2).

4. Discussion

Part of the intrigue surrounding CE is the significant variability in its presentation, and the WHO standardized US classification was developed to address this variability by reflecting disease natural history and allowing for standardization of treatment decisions so that the disease can be most effectively eradicated from affected persons (Brunetti et al., 2010; Solomon et al., 2017c). According to the WHO standardized US classification of CE, there are seven cystic stages of the disease, with each class demonstrating its own distinguishing characteristics. The earliest presumed stage is a cystic lesion (CL), an undifferentiated simple cyst: thought to be an early, simple cyst, it is considered active with the potential to grow and develop (WHO-IWGE, 2003). US characteristics of CE1, CE2, and CE3 cysts are pathognomonic for infection with *E. granulosus*. Active stages of CE include CE1 and CE2, which are usually fertile, containing viable protoscoleces (WHO-IWGE, 2003). CE1 cysts are unilocular, whereas CE2 cysts are either septated or contain daughter cysts (WHO-IWGE, 2003). CE3 cysts are transitional: CE3A cysts demonstrate laminated membrane detachment from the cyst wall, and CE3B cysts contain a mixture of intact and ruptured daughter cysts in a matrix of solid, degenerated materials (WHO-IWGE, 2003). CE4 and CE5 cysts predominantly contain degenerated materials and are considered inactive and infertile (WHO-IWGE, 2003; Gil-Grande et al., 1993).

Given that these disease stages suggest varying levels of parasitic