Diagnostic criteria in renal and hepatic cyst infection

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ABSTRACT

Cyst infection is a severe complication of renal and hepatic cystic disease that frequently leads to hospitalization. In most cases the diagnosis of cyst infection is made empirically as a cyst aspirate is frequently unavailable. This study aims to evaluate diagnostic criteria, microbiological findings and imaging modalities needed to diagnose cyst infection. In order to do so, we evaluated reports that characterize cyst infection cases published in the English language between 1948 and January 2014. We identified 70 articles documenting a total of 215 cyst infection cases (renal n = 119; hepatic n = 96). Six studies, including 74 cases of renal and 61 cases of hepatic cyst infection, used diagnostic criteria. The criteria that led to a definite cyst infection diagnosis were consistent, whereas criteria for a ‘probable diagnosis’ varied considerably. Cyst infection cases commonly have abdominal pain, fever and elevated serum inflammatory markers. Urine and blood cultures frequently remained negative, even in definite cases. The diagnostic properties of 18F-fluorodeoxyglucose positron-emission computed tomography (18F-FDG PET/CT) are probably best to diagnose cyst infection. Cyst aspirate indicating infection is currently the gold standard in diagnosing cyst infection. If not available, a combination of clinical and biochemical parameters is necessary to make a well-considered diagnosis, preferably including 18F-FDG PET/CT.

Keywords: ADPKD, cyst infection, diagnostic criteria, hepatic cyst, renal cyst

INTRODUCTION

Hepatic cysts are defined as cavities containing a clear, bile-like fluid, which arise from abnormal bile duct cells [1]. Simple renal cysts are usually unilateral and located cortically, extending outside the parenchyma and distorting the renal contour [2]. The phenotype of renal and hepatic cystic disease ranges from a solitary cyst to multiple cysts in the context of two distinct genetic disorders: autosomal dominant polycystic kidney disease (ADPKD) and autosomal dominant polycystic liver disease (PCLD) [3–6].

Renal and hepatic cyst infection are considered a severe complication as cyst infections frequently lead to hospitalization and often require invasive treatment [7]. Intuitively, diagnosing cyst infection may seem straightforward, but in clinical practice there is uncertainty and controversy on the best method to use for diagnosis. At present, the gold standard for diagnosing cyst infection is a cyst aspirate with the presence of bacteria and/or neutrophils suggestive of infection [7–9]. However, in most cases a cyst aspirate is unavailable because the infected cyst cannot be identified or the cyst cannot be accessed percutaneously. Therefore, clinicians tend to use a mix of clinical, biochemical and imaging findings to diagnose cyst infection [8,9]. Uncertainty in disease definition is a key contributor to practice variation; hence the need for a unified set of clinical diagnostic criteria.

This article aims to evaluate diagnostic criteria, microbiological findings and imaging modalities that are used to diagnose cyst infection. Therefore, we systematically identified all reports characterizing renal and hepatic cyst infection cases that were published in English between 1948 and January 2014.

METHODS

Literature search

We systematically searched the electronic database of The Cochrane Library, PubMed, Medline and Web of Science using the following keywords: ‘cyst’, and ‘infection’, and ‘liver or kidney’ (Figure 1). We limited our search to articles published in English between 1948 and January 2014. By screening title and abstract we made a selection of articles eligible for inclusion. The remaining articles were retrieved for full text evaluation and reference lists were searched for additional articles. We included published peer-reviewed studies of any design that described diagnostic criteria and/or characterized renal or hepatic cyst infection cases.

Data extraction

The process of data extraction was performed by a single investigator (M.L.). We stratified the obtained data in two categories: probable cyst infection and definite cyst infection.
studies reported both probable and definite diagnostic criteria, cyst infection cases were stratified according to these cyst infection definitions. All cases in which definite diagnostic criteria did not contain positive cyst aspirate culture as diagnostic criterion were defined as probable cyst infection cases. We combined individual cases from studies that did not describe any diagnostic criteria. In line with the gold standard proposed in the literature [7–9], we categorized these cases as definite cyst infection when cyst aspiration led to pathogen isolation; all other cases were categorized as probable cyst infection cases. Continuous variables are expressed as means with standard deviation (±SD) or medians with interquartile range (IQR) depending on the distribution of the data.

Variables
We extracted clinical, biochemical, microbiological and imaging findings of all included cyst infection cases. We scored pain when abdominal discomfort or flank pain was reported in these reports. We assessed whether patients received renal replacement therapy or used immunosuppressive drugs when signs of cyst infection presented themselves. Body temperature is shown in degrees Celsius (°C), serum C-reactive protein (CRP) in mg/L and serum white blood cell count (WBC) in ×10⁹/L. Renal function was estimated by obtaining glomerular filtration rate (GFR) in mL/min/1.73 m². Microbiological cultures were considered positive if cultures led to pathogen isolation.

Imaging
We extracted all radiological and nuclear imaging data from the included studies. We considered imaging results positive for cyst infection when the authors from the original article interpreted these results as suggestive of cyst infection. We extracted data on the use of contrast agents for computed tomography (CT) and magnetic resonance imaging (MRI).
RESULTS

Identification of the literature
We included 70 articles for full text evaluation (Figure 1). We identified six studies that used diagnostic criteria [7, 9–13]. These studies characterized renal (n = 74) and/or hepatic (n = 61) cyst infection cases [7, 9–13]. In addition, we assessed 64 articles that reported individual cases of renal (n = 45) or hepatic cyst infection (n = 35) (Supplementary data). In total, we identified 215 cases of cyst infection (renal n = 119; hepatic n = 96).

Diagnostic criteria in the case of renal and hepatic cyst infection
Table 1 provides an overview of the diagnostic criteria used in cyst infection cases [7, 9–13]. Three studies stratified cyst infection by probable and definite diagnosis [7, 9, 12], whereas three other studies used a single set of clinical diagnostic criteria [10, 11, 13]. The diagnosis of ‘definite’ cyst infection was made when a cyst aspirate contained signs of ‘infection’, i.e. the presence of neutrophils [7], pathogens [9] or a combined presence of neutrophils and pathogens [12]. Given that only a subset of patients underwent cyst aspiration, a definite cyst infection diagnosis could only be established in a minority of cases [7, 9, 12]. In the remaining cases a ‘probable’ cyst infection diagnosis was made.

Criteria for ‘probable’ cyst infection included different combinations of clinical, biochemical, microbiological and/or imaging findings (Table 1). Four studies proposed to diagnose cyst infection after excluding other infectious causes [7, 9, 10, 12]. Clinical findings that are part of the diagnostic criteria include abdominal pain and fever. The definition of abdominal pain ranged from unspecified discomfort to localized pain in the vicinity of the liver or kidney. Different cut-off values for fever were used, ranging from >38°C to >38.5°C. Biochemically, elevated serum CRP (varying from >50 mg/L to >150 mg/L) was commonly used as an indicator of infection [7, 9, 12, 13]. One study included raised serum WBC (>10 x 10⁹/L) as diagnostic criterion [9]. Microbiological findings were part of one set of diagnostic criteria [10]. The researchers suggested that the combined presence of positive urine or blood cultures and refractoriness to ampicillin and aminoglycoside antibiotic treatment indicated cyst infection [10]. Imaging findings from ultrasonography (USG), CT or MRI were used in five studies to support the diagnosis of probable cyst infection [7, 9, 11–13]. In three studies, CT was primarily used to exclude intracystic haemorrhage [7, 9, 12]. ¹⁸Fluorodeoxyglucose positron-emission computed tomography (¹⁸F-FDG PET/CT) was used as a diagnostic tool in one set of diagnostic criteria [13]. Whereas probable diagnostic criteria were chosen empirically in most studies [7, 10–13], one study tried to define these criteria more accurately [9]. This study analysed the clinical findings of cases with a definite diagnosis of either renal or hepatic cyst infection (n = 24) and cases with intracystic haemorrhage (n = 12) [9]. By applying specific cut-off values for body temperature (>38°C), serum CRP (>150 mg/L) and serum WBC (>150 mg/L), this study could correctly identify 76% of cyst infection episodes [9].

Renal cyst infection
Patient characteristics. As shown in Table 2, we characterized 119 renal cyst infection cases (probable n = 81; definite n = 38). Renal cyst infection occurred mainly in the context of ADPKD and it was diagnosed in 91% of probable and 68% of definite cyst infection cases (Supplementary data, Table S1) [7, 9–13]. The remaining definite cyst infections were diagnosed in patients with solitary renal cysts (29%) or multiple renal cysts, not being ADPKD (3%). In the individual cases, ~15% of the patients received renal replacement therapy and/or used immunosuppressive drugs at the time of diagnosis (Table 2).

Clinical and biochemical features. Abdominal pain was documented in 59–88% of renal cyst infection cases (Table 2). Reported values of body temperature (median 39.0°C), serum CRP (median 55–228 mg/L) and serum WBC (median 10.7–17.4 x 10⁹/L) were consistent with the presence of an infection (Table 2).

Microbiological findings. Negative urine (46%) and blood (61%) cultures were frequently seen in renal cyst infection cases (Table 3). In 88% of definitive cyst infection cases with a positive urine culture (n = 8), the urine and cyst aspirate cultures yielded identical pathogens (Supplementary data, Table S2). Likewise, similar pathogens grew from blood and cyst aspirate culture in all definite cyst infection cases with a positive blood culture (n = 6) (Supplementary data, Table S2). In 81% of renal cyst aspirate cultures (n = 52) a pathogen was successfully isolated (Table 3). Overall, *Escherichia coli* (*E. coli*) was most commonly cultured (Table 3).

Radiological findings. As shown in Table 4, USG and CT did not contribute to the diagnosis of probable renal cyst infection cases. However, in four definite cyst infection cases, contrast-enhanced CT produced images that suggest cyst infection. The experience with MRI is limited, as we identified only 11 results. ¹⁸F-FDG PET/CT accurately identified renal cyst infection in all but one of the probable renal cyst infection cases, even when other modalities failed (Supplementary data, Tables S2 and S4). Moreover, ¹⁸F-FDG PET/CT confirmed renal cyst infection in all definite renal cyst infection cases (Table 4).

Hepatic cyst infection
Patient characteristics. We included a total of 96 cases of hepatic cyst infection: 52 were diagnosed as probable infection cases and 44 as definite infection cases (Table 2). Again, ADPKD was most prevalent in both probable (87%) and definite (80%) hepatic cyst infection cases. Solitary hepatic cysts and PCLD were diagnosed in the remainder of cases (Supplementary data, Table S1) [7, 9, 11–13]. As observed in the individual renal cyst infection cases, a high percentage of patients received renal replacement therapy (>10%) and/or used immunosuppressive drugs (>30%) (Table 2) [7, 9, 11, 13].
Clinical and biochemical features. As shown in Table 2, abdominal pain was reported in 59–100% of cases. If documented, body temperature (median 38°C–39.0°C) and serum CRP (median 120–220 mg/L) were indicative of infection. In contrast, serum WBC values were not increased or only slightly elevated (median 7.9–13.2 × 10^9/L).

Microbiological findings. Blood cultures led to successful pathogen isolation in 60% of all hepatic cyst infection cases, whereas 13% of urine cultures returned positive (Table 3). Patients with both a positive blood and cyst aspirate culture (n = 11) had similar pathogens isolated in 82% of all cases (Supplementary data, Table S2). Again, E. coli was the most common isolated pathogen (Table 3).

Radiological findings. USG, CT, MRI and 18F-FDG PET/CT were utilized when there was suspicion of hepatic cyst infection (Table 4). Similar to the results obtained in renal cyst infection cases, USG and CT were of limited use in diagnosing hepatic cyst infection (Table 4). However, contrast-enhanced CT was indicative of cyst infection in 60% of definite cases (Table 4). The use of MRI is limited; only seven cases have
Table 2. Patient characteristics of renal and hepatic cyst infection cases

<table>
<thead>
<tr>
<th>Origin (study)</th>
<th>Diagnosis (Pts)</th>
<th>M (%)</th>
<th>Age (years, median, IQR)</th>
<th>GFR (mL/min/1.73m², median, IQR)</th>
<th>RRT (%)</th>
<th>ISD (%)</th>
<th>Abdominal pain (%)</th>
<th>Body temperature (°C, median, IQR)</th>
<th>CRP (mg/L, median, IQR)</th>
<th>WBC ($\times 10^9$/L, median, IQR)</th>
<th>UC+ (%)</th>
<th>BC+ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic criteria studies</td>
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</tr>
<tr>
<td>Schwab et al. [10]</td>
<td>Renal Prb (15)a</td>
<td>13</td>
<td>49 (31–59)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>73</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>Suwabe et al. [11]</td>
<td>Renal Prb (15)a</td>
<td>80</td>
<td>60.0 ± 6.3</td>
<td>NA</td>
<td>87</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>199 ± 103</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hepatic Prb (28)a</td>
<td>39</td>
<td>61.8 ± 7.2</td>
<td>NA</td>
<td>82</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>181 ± 105</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Sallée et al. [7]</td>
<td>Renal Prb (24)</td>
<td>46</td>
<td>44b</td>
<td>60b</td>
<td>17</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>168b</td>
<td>10.7b</td>
<td>56</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Dfn (6)</td>
<td>67</td>
<td>53b</td>
<td>33b</td>
<td>33</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>205b</td>
<td>17.4b</td>
<td>33</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>Hepatic Prb (4)</td>
<td>50</td>
<td>67b</td>
<td>RRT</td>
<td>100</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>161b</td>
<td>7.9b</td>
<td>NA</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Dfn (2)</td>
<td>50</td>
<td>67b</td>
<td>RRT</td>
<td>100</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>Jouret et al. [12]</td>
<td>Renal Prb (3)</td>
<td>33</td>
<td>56 ± 5</td>
<td>[9, 10, 65]</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>260 ± 140</td>
<td>13.2 ± 5.8</td>
<td>67</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>Hepatic Dfn (3)</td>
<td>40</td>
<td>61 ± 13</td>
<td>49 ± 17</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>230 ± 80</td>
<td>8.6 ± 4.6</td>
<td>0</td>
<td>40</td>
</tr>
<tr>
<td>Piccoli et al. [13]</td>
<td>Renal Prb (5)c</td>
<td>40</td>
<td>68 (60–80)</td>
<td>35 (22–71)</td>
<td>0</td>
<td>0</td>
<td>80</td>
<td>NA</td>
<td>55 (18–230)</td>
<td>NA</td>
<td>60</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Hepatic Prb (1)c</td>
<td>0</td>
<td>60</td>
<td>RRT</td>
<td>100</td>
<td>0</td>
<td>100</td>
<td>38</td>
<td>120</td>
<td>NA</td>
<td>0</td>
<td>NA</td>
</tr>
<tr>
<td>Suwabe et al. [9]</td>
<td>Renal Dfn (6)</td>
<td>83</td>
<td>57 (48–65)</td>
<td>NA</td>
<td>83</td>
<td>NA</td>
<td>59d</td>
<td>39.0 (38.5–39.6)d</td>
<td>220 (184–273)d</td>
<td>13.2 (10.3–19.1)d</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>Hepatic Dfn (18)</td>
<td>39</td>
<td>62 (58–67)</td>
<td>NA</td>
<td>72</td>
<td>NA</td>
<td>59d</td>
<td>39.0 (38.5–39.6)d</td>
<td>220 (184–273)d</td>
<td>13.2 (10.3–19.1)d</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Individual cases: data are presented when more than five cases reported the variable of interest (Supplementary data shows individual case data)</td>
<td></td>
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</tr>
<tr>
<td>All</td>
<td>Prb (33)</td>
<td>36</td>
<td>53 (41–62)</td>
<td>NA</td>
<td>15</td>
<td>33</td>
<td>73</td>
<td>39.0 (38.5–39.5)</td>
<td>186 (61–281)</td>
<td>13.2 (9.0–17.1)</td>
<td>27</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>Dfn (47)</td>
<td>45</td>
<td>57 (40–66)</td>
<td>NA</td>
<td>15</td>
<td>21</td>
<td>89</td>
<td>39.0 (38.4–39.8)</td>
<td>226 (126–275)</td>
<td>14.5 (10.0–18.7)</td>
<td>21</td>
<td>36</td>
</tr>
<tr>
<td>Renal</td>
<td>Prb (19)</td>
<td>32</td>
<td>45 (32–53)</td>
<td>NA</td>
<td>16</td>
<td>21</td>
<td>79</td>
<td>39.0 (38.5–39.5)</td>
<td>187 (71–277)</td>
<td>15.3 (10.0–17.8)</td>
<td>42</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Dfn (26)</td>
<td>35</td>
<td>50 (36–61)</td>
<td>NA</td>
<td>19</td>
<td>12</td>
<td>88</td>
<td>39.0 (38.4–40.3)</td>
<td>228 (122–262)</td>
<td>15.2 (11.9–21.3)</td>
<td>31</td>
<td>23</td>
</tr>
<tr>
<td>Hepatic</td>
<td>Prb (14)</td>
<td>43</td>
<td>63 (55–69)</td>
<td>NA</td>
<td>14</td>
<td>50</td>
<td>64</td>
<td>NA</td>
<td>185 (30–300)</td>
<td>10.6 (4.4–13.3)</td>
<td>7</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Dfn (21)</td>
<td>57</td>
<td>65 (58–70)</td>
<td>NA</td>
<td>10</td>
<td>33</td>
<td>90</td>
<td>38.8 (38.5–39.7)</td>
<td>216 (125–321)</td>
<td>12.0 (9.6–17.2)</td>
<td>10</td>
<td>52</td>
</tr>
</tbody>
</table>

NA, not available; Prb, probable; Dfn, definite; Pts, patients; M, male; IQR, interquartile range; RRT, renal replacement therapy; ISD, immunosuppressive drugs; CRP, serum C-reactive protein; WBC, serum white blood cell count; UC+, positive urine cultures; BC+, positive blood cultures, GFR, glomerular filtration rate. Continuous data are expressed as medians with IQR or means with standard deviation (±SD).

aPatients with a positive cyst aspirate (bacteria cultured) were not separately documented; therefore, all patients were categorized as probable cyst infection.

bOnly the median was reported.

cOnly 18F-FDG PET/CT positive cases are presented.

dResults of renal and hepatic cyst infection patients were not separately documented; therefore, data are presented in both renal and hepatic cyst infection groups.
As cyst aspirates are only available for a limited number of patients, a set of diagnostic criteria is needed to establish a (probable) cyst infection diagnosis [7, 9–13]. The problem is that these criteria are variable and poorly validated [7, 10–13]. We identified one study that validated diagnostic criteria in a dataset of cases with either a cyst infection or intracystic haemorrhage, but external generalization of these criteria is limited by the high number of patients receiving renal replacement therapy at the time of diagnosis [9]. Due to the considerable heterogeneity between studies, we could not perform a pooled calculation of sensitivity and specificity for the detection of cyst infection with individual diagnostic parameters. Our results do clearly show that abdominal pain (89%), fever (median 39.0°C) and increased serum CRP (median 226 mg/L) are important

**DISCUSSION**

This review evaluates the diagnostic approach to renal and hepatic cyst infection. The definition of the proposed gold standard is consistent in the literature: a cyst aspirate containing white blood cells and pathogens (Table 1) [7, 9, 12]. As cyst aspirates are only available for a limited number of patients, a set of diagnostic criteria is needed to establish a (probable) cyst infection diagnosis [7, 9–13]. The problem is that these criteria are variable and poorly validated [7, 10–13]. We identified one study that validated diagnostic criteria in a dataset of cases with either a cyst infection or intracystic haemorrhage, but external generalization of these criteria is limited by the high number of patients receiving renal replacement therapy at the time of diagnosis [9]. Due to the considerable heterogeneity between studies, we could not perform a pooled calculation of sensitivity and specificity for the detection of cyst infection with individual diagnostic parameters. Our results do clearly show that abdominal pain (89%), fever (median 39.0°C) and increased serum CRP (median 226 mg/L) are important
Table 4. Imaging results in renal and hepatic cyst infection cases: diagnostic criteria studies and individual cases combined

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>USG</th>
<th>CT*</th>
<th>Contrast-enhanced CT</th>
<th>MRI*</th>
<th>Contrast-enhanced MRI</th>
<th>DWI</th>
<th>18F-FDG PET/CT</th>
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</thead>
<tbody>
<tr>
<td><strong>All</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Probable</td>
<td>13 (5/38)</td>
<td>20 (12/59)</td>
<td>36 (4/11)</td>
<td>58 (7/12)</td>
<td>100 (4/4)</td>
<td>100 (1/1)</td>
<td>93 (26/28)</td>
</tr>
<tr>
<td>Definite</td>
<td>58 (14/24)</td>
<td>62 (24/39)</td>
<td>78 (7/9)</td>
<td>83 (5/6)</td>
<td>100 (1/1)</td>
<td>100 (1/1)</td>
<td>100 (10/10)</td>
</tr>
<tr>
<td><strong>Renal cyst infection</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Probable</td>
<td>12 (3/26)</td>
<td>18 (7/40)</td>
<td>33 (2/6)</td>
<td>57 (4/7)</td>
<td>100 (3/3)</td>
<td>100 (1/1)</td>
<td>92 (12/13)</td>
</tr>
<tr>
<td>Definite</td>
<td>60 (9/15)</td>
<td>75 (15/20)</td>
<td>100 (4/4)</td>
<td>100 (4/4)</td>
<td>100 (1/1)</td>
<td>100 (1/1)</td>
<td>100 (4/4)</td>
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<td><strong>Hepatic cyst infection</strong></td>
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</tr>
<tr>
<td>Probable</td>
<td>17 (2/12)</td>
<td>26 (5/19)</td>
<td>40 (2/5)</td>
<td>60 (3/5)</td>
<td>100 (1/1)</td>
<td>NA</td>
<td>93 (14/15)</td>
</tr>
<tr>
<td>Definite</td>
<td>56 (5/9)</td>
<td>47 (9/19)</td>
<td>60 (3/5)</td>
<td>50 (1/2)</td>
<td>NA</td>
<td>NA</td>
<td>100 (6/6)</td>
</tr>
</tbody>
</table>

NA, not available; n, number; USG, ultrasonography; CT, computed tomography; MRI, magnetic resonance imaging; DWI, diffusion-weighted imaging; 18F-FDG PET/CT, 18fluorodeoxyglucose positron-emission computed tomography. Supplementary data shows individual case data.

*All results combined (contrast-unenhanced, contrast-enhanced and results without specific documentation regarding contrast use).

indicators of cyst infection and should therefore be included in diagnostic criteria (Table 2). Although it seems intuitive to do so, our data questions the usefulness of microbiological cultures (Table 1). Most urine and blood cultures remained negative, even in patients with a definite cyst infection diagnosis (Table 2). Although valuable in tailoring the choice of antibiotics, there is no evidence to support the use of routine microbiological cultures during the diagnostic work-up of patients suspected of cyst infection.

Reliable, non-invasive diagnostic markers and imaging techniques that indicate cyst infection would be valuable in reducing the need for invasive interventions. Cancer antigen 19-9 (CA 19-9) is under investigation as a biomarker for hepatic cyst infection [14]. One study found that serum CA 19.9 was elevated in 40% of ADPKD patients with hepatic cyst infection [14]. As CA 19-9 is known to be elevated in patients with polycystic liver disease [15], a patient-specific cut-off value is necessary before CA 19-9 can be used as a reliable marker of infection [14]. Imaging techniques could prove to be a helpful tool to diagnose cyst infection, but our results indicate that conventional imaging is of limited use. USG and CT were negative in ~40% of scans performed in definite cyst infection cases (Table 4). Contrast-enhanced CT and MRI were diagnostic in up to 100% of scans, but the experience with these techniques is limited. Moreover, the use of contrast agents in ADPKD patients with impaired renal function is relatively contraindicated [8, 16]. Recent technological advances have made diffusion-weighted imaging (DWI) a valuable MRI technique in renal and hepatic lesion evaluation [8, 9, 17]. In brief, DWI expresses the rate of water molecule diffusion between tissues, given as the apparent diffusion coefficient (ADC) [18]. A marked decrease in the ADC value is thought to indicate cyst infection [8, 9]. However, established ADC threshold values indicating cyst infection are lacking, which limits the clinical applicability. 18F-FDG PET/CT is a promising imaging technique that is minimally labour intensive, has a high contrast ratio and a low inter-observer variability [8, 12, 13, 16]. As it offers the ability to localize infected cysts, 18F-FDG PET/CT helps in differentiating renal from hepatic cyst infection. Furthermore, follow-up 18F-FDG PET/CT is potentially useful in tailoring antibiotic treatment by evaluating individual treatment response [13]. In our study, cyst infection was identified in 100% of definite and 93% of probable cyst infection cases by 18F-FDG PET/CT (Table 4).

Moreover, in two cases the failure of 18F-FDG PET/CT to correctly identify cyst infection was probably due to suboptimal technical conditions [12]. Therefore, 18F-FDG PET/CT presents a powerful tool to bolster the diagnosis of cyst infection. Nonetheless, well-designed studies need to be performed to determine the exact diagnostic sensitivity and specificity of 18F-FDG PET/CT across a wide spectrum of disease presentations. Ultimately, the use of 18F-FDG PET/CT is restricted due to high costs and limited availability.

Combining clinical and biochemical parameters is needed to make a well-considered diagnosis of cyst infection. Establishing specific cut-off values for the infection parameters (fever, serum CRP) and diagnostic markers (CA 19–9, DWI, 18F-FDG PET/CT) is necessary, but may encounter difficulties due to clinical heterogeneity among cyst infection patients.

The main strength of this study is that it offers a review of the available diagnostic criteria concerning cyst infection and characterizes 215 published cyst infection cases. A potential limitation is that the generalization of our findings is affected by publication bias. Furthermore, the included studies applied variable diagnostic criteria to establish cyst infection diagnosis, which potentially lead to a heterogeneous defined population. On the other hand, the variation in diagnostic criteria observed in these studies is comparable with the variation seen in clinical practice. It remains difficult to differentiate clinically between renal and hepatic cyst infection. Therefore, it is possible that cases were misdiagnosed. However, the fact that we did not observe evident differences between definite and probable cyst infection patients implies that this cannot have greatly affected our results.

To conclude, a cyst aspirate indicating infection is the current gold standard in diagnosing renal and hepatic cyst infection. Should a cyst aspirate be unavailable, combining clinical and biochemical parameters is mandatory. If available,
18F-FDG PET/CT can be used to support a cyst infection diagnosis.

**SUPPLEMENTARY DATA**

Supplementary data are available online at http://ndt.oxfordjournals.org.

**ACKNOWLEDGEMENTS**

The authors wish to thank Dirk Pesman from the Department of English Language and Linguistics Radboud University Nijmegen, the Netherlands, for his advice.

**CONFLICT OF INTEREST STATEMENT**

None declared.

**REFERENCES**


Received for publication: 29.11.2013; Accepted in revised form: 27.5.2014