Cyst infection in polycystic kidney disease: a clinical challenge

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Introduction

With a prevalence of 1 : 500–1 : 1000, autosomal dominant polycystic kidney disease (ADPKD) accounts for 4–10% of patients on dialysis. Significant advances in the genetics and pathophysiology of ADPKD have been made over the years, and its complications are well documented. Infection remains one of the commonest of these.

Lower urinary tract infection and pyocystis

Symptomatic lower urinary tract infection affects 50–75% of all polycystic patients at some time. Treatment is simple and the condition is usually uncomplicated. Infection of the upper urinary tract is different, however. An autopsy study by McNamara in 1965 showed evidence of pyelonephritis in 56% of patients with ADPKD, even though clinical sepsis was not considered to be significant in many of these cases [1]. The infection of a single cyst within a polycystic kidney—pyocystis—is a well-recognized and potentially serious complication of ADPKD.

Cyst infection probably originates from the lower urinary tract, a theory that is supported by the observation that up to 92% of upper tract infections occur in females [2]. The infecting organisms are very similar to those causing lower urinary tract infections—the enterobacteriaceae. Treatment can be difficult, and significant morbidity, mortality and complications, notably the development of perinephric abscesses, have been described [3]. Diagnosis is not always simple, and supportive diagnostic aids such as imaging modalities are lacking. The choice of antibiotic for use in cyst infection can be difficult because of uncertainty over the diagnosis, penetration of antibiotics into cysts and fluid, and potentially resistant organisms. Sporadic research on the topic was reported from 1981 to the early 1990s, but interest in the topic has waned. It is therefore timely to re-examine this work.

The microbes

Microbiological results from small case series and anecdotal reports confirm that the commonest organisms involved in cyst infections are *Escherichia coli*, *Klebsiella*, *Pseudomonas* and *Proteus* species [4]. Infections with staphylococci [5] and streptococci [2] are rare, tuberculous and fungal disease even more so. The potential for haematogenous infection is supported by occasional reports, for example, of staphylococcal infection of a cyst in an intravenous drug abuser [5]. Anaerobic infection is uncommon, but perinephric abscesses [3] and aspirated cyst fluid have grown anaerobes [6]; the finding of low oxygen tensions within some cysts would support the potential for anaerobic infections [4].

Clinical presentation

Infection of the lower urinary tract and acute pyelonephritis in a patient with polycystic kidney disease are not usually diagnostic dilemmas; the same cannot be said for pyocystis. The clinical presentation is classical of a discrete area of tenderness relating to one kidney. Torsion of or haemorrhage into a cyst may, however, present similarly. A more difficult challenge is the assessment of the significance of bacteremia in an ADPKD patient with only equivocal clinical signs. Many cysts do not communicate with the rest of the urinary tract and, therefore, associated lower urinary tract symptoms and bacteriuria may be absent. In a series of 15 such patients investigated by Schwab [2], however, attempts to isolate an organism from blood and urine were always successful. Furthermore, four patients from this group required nephrectomy which confirmed that cyst infection was caused by the same organism as that in blood or urine. If necessary, puncture of a suspicious cyst under ultrasonographic guidance may also be diagnostic.

Diagnostic problems

Diagnostic imaging is often less helpful than might be expected. Despite advances in available modalities, imaging of polycystic kidneys remains a problem, and attempts to find a single infected cyst therein is a ‘radiologist’s nightmare’. Polycystic kidneys often contain multiple cysts with very different contents, and pus and organizing haematomas can look very similar when scanned. Ultrasound, computed tomography and magnetic resonance imaging scanning image cystic kidneys well, but the confident identification of an infected cyst is often impossible. Radioisotope studies
Penetration of antibiotics into cysts

Antibiotic treatment of infected cysts has variable effects; cure can be rapid, but resistant infection requiring radical intervention has been described. The reason for this is thought to relate to the transport characteristics of individual cysts and was first studied in detail by Muther and Bennett, who aspirated and analysed the contents of individual cysts from polycystic kidneys removed at nephrectomy or autopsy [7]. In each case, antibiotics had been given for 36–48 h before operation, but in only two cases was there thought to be an infected cyst. By calculating the cyst:sodium ratio, all cysts were divided into proximal (ratio > 0.9) or distal (<0.2). Analyses of antibiotic concentrations in these cysts demonstrated that gentamicin, tobramycin and ticarcillin were undetectable in distal cysts, and in these cysts demonstrated that gentamicin, tobramycin, and ticarcillin were undetectable in distal cysts, and only cephapirin was found in these cysts. Tobramycin was not found in proximal cysts either, whilst gentamicin and ticarcillin were. These findings bring into question the mechanism by which antibiotics might enter cysts.

Microdissection reveals that cysts of tubular origin communicate with the glomerulus proximally. One might suspect, therefore, that an antibiotic that is filtered at the glomerulus might accumulate in a cyst to the concentrations seen; quantitative studies, however, do not support this. Several authors previously have noted that even a single healthy nephron filtering 1 ml of filtrate to a cyst, and this is not enough to explain the antibiotic accumulation seen [7,8]. The inevitable conclusion is that much movement of antibiotics into cysts is transepithelial.

Whilst the exact mechanism of cyst development remains unknown, it is recognized that cysts retain some of the histological and physiological characteristics of the epithelium from which they seem to develop. Most cysts are 'non-gradient', and are thought to be derived from proximal tubular epithelial cells, between which are only loose apical junctions and leaky paracellular channels. Solute access to these cysts is by diffusion, and cyst contents are similar in composition to plasma. Active mechanisms to transport organic anions are found in some non-gradient cysts, but are not invariable.

Distal cysts, by contrast, are able to sustain considerable solute gradients. These cysts are composed of distal tubular cells which are joined by tight intercellular junctions, across which diffusion is severely limited. Hydrophilic lipid-insoluble antibiotics penetrate these cysts poorly, as might be expected; the transport of lipophilic antibiotics is not uniform, however, as the mechanisms for this are influenced by cyst fluid pH and the diffusion constant (pKₐ) of the antibiotic used.

In a study of clindamycin accumulation in cysts, Schwab demonstrated that concentrations of the drug rose as cyst fluid pH fell, and related this to a relatively alkaline pKₐ of 7.45 [8]. At a physiological pH, unbound drug will be almost one half ionized and one half not; being a lipophilic antibiotic, the non-ionized half will move relatively freely into cysts. Once inside a cyst, an acidic environment would result in ionization of the previously non-ionized half, thus making back-diffusion out of the cyst difficult (ion trapping). Extrapolation of this concept would also suggest that anionic antibiotics, notably the β-lactams (which are also lipophobic), would not enter an acidic cyst. The conclusion from this work was that drugs with an alkaline pKₐ should be used for cyst infections but, with cyst pH varying from 5 to 7.6, it is hard to be dogmatic with regards to this. Clindamycin levels in cysts of neutral pH approached very low levels comparable with the lipophobic antibiotic gentamicin; the benefit of the higher pKₐ is obviously lost in this situation.

Practical guidelines for the selection of antibiotics

What, therefore, are the ideal characteristics of an antibiotic for use in cyst infection? In the absence of microbiological sensitivities, activity against Gram-negative bacteria is essential. High bioavailability, widespread distribution throughout body fluids and lipid solubility would be desirable. This simple set of requirements is actually surprisingly difficult to achieve, as illustrated in Table 1.

A final caveat to this is that much of the above comes from work on uninfected cysts. The pharmacokinetics of infected cysts may well be very different, and indeed one study has demonstrated that the normally non-penetrating aminoglycoside amikacin can be found inside infected cysts [10]. The choice of antibiotic to use in treating an infected polycystic kidney therefore remains an issue of debate. Current guidance suggests that systemic sepsis be

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Lipid soluble?</th>
<th>Active against Gram-negative enteric pathogens?</th>
<th>Shown to accumulate in cyst fluid, or documented as curing cyst infection?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloramphenicol</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Co-trimoxazole</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>✓</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>✓</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>✓</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>✓</td>
<td>✗</td>
<td>✓</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>✗</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>✗</td>
<td>✓</td>
<td>✗</td>
</tr>
</tbody>
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Adapted from Sklar et al. [4] and Elzinga and Bennett [9].
treated with intravenous ampicillin and an aminoglyco-
side, whilst recognizing that the failure of aminoglyco-
sides in particular to penetrate cysts be used almost as a
diagnostic tool. Failure to respond to these antibiotics
would, therefore, suggest cyst infection, and therapy
should be adjusted appropriately. With their potential
for toxicity, however, aminoglycosides may be withheld,
particularly when renal function is compromised; cip-
rofloxacin would appear to be a reasonable alternative.
One case report has demonstrated its efficacy where
other antibiotics have failed [11], and local experience
has found it to be useful in at least two cases. Where
a cure seems impossible, intervention may be required,
by surgical or radiological drainage, or the release of
obstruction. In severe cases, or those with persistent
recurrent infection, nephrectomy may be required.

The changing pattern of cyst infection

Within our practice, the need for drastic measures in
controlling pyocystis has declined considerably over the
years; indeed the incidence of serious infection
complicating ADPKD seems to be decreasing. A 1983
study of polycystic patients identified an infection rate
of 26%, nephrectomy being needed in 45% and death
occurring in 7% [12]. A similar study in 1996 suggested
rates of 16, 12 and 0% respectively [13]. The reasons
for this are not known, but can be speculated. The
knowledge gained from reported studies and the use
of newer antibiotics may have had its impact, as will
have improved microbiological services. The rapid
treatment of lower urinary tract infection by primary
care services in the community, and the widespread
use of antibiotics as part of the treatment of acute
episodes of loin pain may well have been a major
influence.

Control of serum phosphate in patients with renal failure—
new approaches

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Introduction

Impaired phosphate excretion with resulting hyper-
phosphataemia is one of the earliest consequences of
chronic renal failure. Hyperphosphataemia plays an
important role in the development of secondary hyper-
parathyroidism. Both secondary hyperparathyroidism
and high serum phosphate levels (in association with
hypercalcaemia in some cases) are associated with
significant morbidity. Consequently, prevention and
treatment of hyperphosphataemia is one of the major
treatment goals of chronic renal failure.

References