Optimal treatment of leptospirosis: queries and projections

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Abstract

Although the global burden of leptospirosis remains enormous and new aspects of the disease are constantly recognised, little progress has been achieved in the field of leptospirosis therapeutics and queries regarding the utility of antibiotics in the late severe form of the disease remain. From the currently existing data, conclusions on the efficacy of antibiotic administration in severe or late disease cannot easily be drawn, since clinical trials have different selection criteria and may focus on \textit{Leptospira} serovars with different virulence. However, as a rule the benefit of the doubt should apply. Moreover, new options, such as ceftriaxone, have a superior safety profile to penicillin. In vitro studies have outlined potential antimicrobial candidates such as macrolides and ketolides. Development of a globally accepted subunit vaccine for humans is warranted but is not expected in the near future.

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1. Introduction

Leptospirosis is a globally distributed anthropozoonosis [1] that has been continuously resurfacing into the epicentre of scientific interest in the last decade. Recognition of a distinct form of clinical presentation, haemorrhagic pulmonary involvement [2], awareness of the risks of disease urbanisation [3], evolution of a new outbreak trend through international recreational exposure [4] and sequencing of the genome of \textit{Leptospira interrogans} [5] have all raised interest in the disease in the last few years, yet progress on treating leptospirosis has been minimal. This is surprising for a ubiquitous disease with thousands of cases annually worldwide. As a consequence, old dilemmas regarding leptospirosis treatment still prevail. New information, either experimental or clinical, rarely emerges, and an as yet inadequately understanding of the pathophysiology of the disease imposes a further obstacle to advances in the field of leptospirosis therapeutics.

2. The pathogen and its epidemiology

There are 17 species, at least 8 pathogenic, and more that 300 serovars (>230 pathogenic) of the genus \textit{Leptospira}. The global distribution of species and serovars varies widely, whilst potential differences in virulence between pathogenic serovars has been entertained but not outlined. \textit{Leptospira interrogans} remains the most prevalent cause of human leptospirosis worldwide [6].

Two widely endemic zones for leptospirosis exist: the first is the Caribbean and Latin America and the second includes most of the countries and islands of the Indian Ocean and the Pacific [6,7]. In Europe the disease is rare, mostly reported from Eastern European and Mediterranean countries [8,9]. Transmission occurs through contact with soil or fresh water contaminated by infected animal urine or by direct contact with infected animal tissues. Portals of entry can be either skin, abrasions, the respiratory tract through inhalation of infectious particle-containing dust or the gastrointestinal tract through ingestion of contaminated water. Populations at risk include abattoir and food industry workers, dairy workers (contact with serovar hardjo-infected cows), rice and sugarcane farmers, sewage workers and miners [10], homeless...
people, flood victims and refugees [11,12] and, finally, adventure travellers [13,14] and military personnel [15]. Numerous animals can serve as carriers, the most important being canine, murine and cattle species [16]. Vaccines for animals exist, but the constant modification of prevalent *Leptospira* species and serovars in certain regions precludes total protection; moreover, vaccination may not prevent animal leptospiuria and the consequent environmental contamination and human risk [17].

### 3. Pathogenesis and clinical presentation

Little is known about the exact pathogenic events taking place in infection by leptospiira. Briefly, following entry and invasion of the bloodstream, disruption of the cell membrane of small vessel endothelia ensues (a toxin-like effect), leading to organ haemorrhage and ischaemia as well as persistence in specific anatomical sites such as the renal tubules. The immunological reaction varies, with both humoral and cellular immunity required for an adequate response. The causative role of the immune response in the development of severe disease is undoubtedly important yet vague.

The majority of patients, especially in endemic areas, do not develop a clinical syndrome. Of those with symptoms, 90% present with a flu-like, self-remitting disease that can easily run undetected. Five to nine percent develop a moderate clinical syndrome requiring hospitalisation, and 1–5% develop the severe form of leptospirosis, usually manifested as the icterohaemorrhagic Weil’s syndrome. Central nervous system involvement and the already-mentioned severe pulmonary haemorrhagic form are also forms of severe leptospirosis, the latter usually being an early event. Although the disease is classically described as biphasic, the second, immune-mediated phase characterised by, among others, aseptic meningitis and ophthalmic involvement is not invariably observed.

### 4. Treatment principles

Choosing an optimal regimen for leptospirosis is a difficult task for a variety of reasons. Some of these were outlined during an attempt by the Cochrane Database System to assess the value of antibiotic treatment of late leptospirosis [18]; numerous other queries remain. First, the relative virulence of pathogenic species and serovars has been understudied, thus precluding the application of results of regional clinical trials with specific leptospiral endemicity to other regions with a different leptospiral endemic profile, at least until a common pattern of virulence can be proved. Second, we still do not understand many important aspects of the disease pathogenesis, and although *L. interrogans* genome sequencing will undoubtedly facilitate improvement of our understanding of

<table>
<thead>
<tr>
<th>Year/country</th>
<th>Antibiotic used</th>
<th>Comments</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1984, US (army)</td>
<td>Doxycycline</td>
<td></td>
<td>Improvement in duration and severity of disease, effect on leptospiruria</td>
<td>[19]</td>
</tr>
<tr>
<td>1988, Barbados</td>
<td>Penicillin</td>
<td>Jaundice was considered indication of severe disease</td>
<td>No statistically significant benefit in mortality and clinical course.</td>
<td>[20]</td>
</tr>
<tr>
<td>1988, US Navy, Philippines</td>
<td>Penicillin</td>
<td>Symptom duration &gt;4 days was inclusion criterion; patients with anuria excluded</td>
<td>Reduced duration of illness, no mortality in treated and controls</td>
<td>[21]</td>
</tr>
<tr>
<td>2000, Brazil</td>
<td>Penicillin</td>
<td>Patients with renal failure included</td>
<td>No benefit in mortality and disease duration</td>
<td>[22]</td>
</tr>
<tr>
<td>2001, US (Hawaii)</td>
<td>Penicillin, other</td>
<td></td>
<td>Antibiotic benefit in illness duration if administered before Day 8</td>
<td>[23]</td>
</tr>
<tr>
<td>2003, Brazil</td>
<td>Penicillin</td>
<td>Symptom duration &gt;4 days and WHO probability score used for inclusion</td>
<td>Mortality double in treated patients</td>
<td>[24]</td>
</tr>
<tr>
<td>2003, Thailand</td>
<td>Ceftriaxone</td>
<td></td>
<td>Ceftriaxone comparable with penicillin in fever duration and mortality</td>
<td>[25]</td>
</tr>
<tr>
<td>2004, Thailand</td>
<td>Penicillin, doxycycline, cefotaxime</td>
<td></td>
<td>Cefotaxime and doxycycline comparable with penicillin in mortality and disease course</td>
<td>[26]</td>
</tr>
<tr>
<td>2006, Greece</td>
<td>Ceftriaxone</td>
<td>Severe defined as two or more of jaundice, renal impairment, respiratory involvement and central nervous system involvement</td>
<td>No control group. Ceftriaxone convenient, mortality only in respiratory involvement</td>
<td>[27]</td>
</tr>
</tbody>
</table>

WHO, World Health Organization.
the disease, the progress made so far is disappointing compared with other zoonotic infections. This leads us to another common obstacle applicable to most zoonoses, namely the lack of funds to study their prevalence in the developing world and their exotic status for industrialised countries; some zoonoses are ‘fortunate’ enough to be considered potential biological weapons and thus may raise interest, but leptospira are not amongst them. Lack of funds and endemicity in countries with limited health infrastructure further leads to limited organised clinical trials. These trials, summarised in Table 1, are further marred by the absence of a common definition for severe leptospirosis; thus, it is not surprising that results are often contradictory. Utilisation of in vitro data and animal models could serve to fill in some of the blanks, but again data are limited (summarised in Table 2) and often contradict in vivo observations.

However, the most difficult task in evaluating the optimal treatment in leptospirosis remains the absence of a common language spoken between scientists. Although the multiple disease forms are acknowledged, where one form ends and another begins is not clear. For example, it is generally accepted that the most common form of the disease may run subclinically and self-remit. Even mild clinical forms may not need antibiotic treatment and may self-remit. However, given the potential of the disease for evolution to a more severe phase, antibiotic treatment is usually administered upon diagnosis. In a classic clinical trial [19], doxycycline proved efficient in reducing the severity and duration of disease upon early administration. Although the term ‘early’ was adequately defined (4 days), the ‘clinical’ term was ill defined as the presence of protean symptoms, thus subject to patient reporting and possible co-existence of other infectious diseases that may in fact cause these symptoms. Co-infection is not a random event, as shown in endemic areas [40,41].

### 4.1. Antibiotics used

As already stated, doxycycline has been effective in decreasing both disease duration and severity. In treating mild clinical forms of leptospirosis, β-lactams such as penicillin and amoxicillin are also useful.

The most controversial aspect of leptospirosis treatment remains the utility of antibiotics in severe and late leptospirosis. The terms ‘severe’ and ‘late’ have often been used interchangeably and, as Table 1 outlines, the definition varies even for the term ‘severe’. The background of this dispute is based on the notion that protracted clinical disease is de facto severe, or prone to development of severe complications. Late disease is synonymous with the second phase of leptospirosis, which is largely considered an immune-
mediated event, therefore antibiotic treatment might be useless and immunomodulation might be the optimal approach. However, what has not been answered is whether this second phase is purely an immune-mediated event. Taking into account that bacterial load is still traceable in this second phase (at least in the form of leptospirosis, for example), it seems logical that bacterial presence must be eliminated at least in order to cease triggering the immune-mediated cascade. But is this immune cascade in need of constant triggering or is it an independent event that, once started, proceeds irrespective of eradication of the pathogen? Clarification of pathogenic events will definitely allow for better understanding of this process. The studies summarised in Table 1 show that penicillin is the major antibiotic used in the later stages of leptospirosis. Emerging literature also supports the use of third-generation cephalosporins, usually ceftriaxone but also cefotaxime. A case report of ceftazidime use in treating leptospirosis also exists [42]. Ampicillin and piperacillin have also been advocated. Aminoglycosides have historically been considered [43], but the potential induction of nephrotoxicity precludes their use in leptospirosis. Administration of ciprofloxacin in a patient with leptospirosis has been reported [44], but the patient also received doxycycline therefore no conclusions can be elicited on fluoroquinolone efficacy.

Can one draw any results from the existing studies? The answer is negative; the results are contradictory, may not refer to all leptospira pathogenic species and the overall number of studies is small and aimed at different patient sub-populations. The advantages of ceftriaxone seem obvious: a convenient once-daily dosing schedule with no need for adjustment in renal failure and the potential to empirically treat other life-threatening conditions that may mimic the clinical presentation of severe leptospirosis. The benefit of the doubt should direct the clinician’s therapeutic choices; if antibiotics are potentially useful in a disease state with significant mortality, antibiotic administration is ethical, since the hazards imposed by their use do not override the potential benefit. Once more, ceftriaxone appears more appropriate, safer than penicillin in all settings and without the risk (at least it has not been reported) of Jarisch–Herxheimer reaction, which may complicate penicillin treatment [45].

Table 2 shows that in vitro studies and animal models may not be as useful in predicting in vivo events. This can be an obstacle when searching for other antibiotic classes that could be utilised in leptospirosis. Penicillin characteristically often shows inadequate inhibitory or bactericidal concentrations, whilst clindamycin, macrolides and ketolides have been reported to be of potential utility; the road to clinical trials may be long enough.

4.2. Special measures

The severe haemorrhagic pulmonary form of leptospirosis is a recently recognised entity that may possess different pathogenic characteristics to classical leptospirosis [46]. Little is known about its treatment principles: a small study reported excellent results with the use of desmopressin [47], whilst others have suggested that inhalation of nitric oxide [48] or corticosteroid pulses [49] may be beneficial. Haemofiltration has also been used in cases accompanied by renal failure [50]. Plasma exchange has been suggested as useful in cases of severe protracted jaundice [51].

5. Prevention

Prevention of leptospirosis can be achieved either by elimination of the environmental risk, by pre-emptive development of protection through vaccination or by prophylactic administration of antibiotics in susceptible populations.

As already noted, environmental control of leptospirosis is a futile target, since the ecology of the species and serovars continually evolves, partly owing to animal vaccination strategies [52]. Risk factors for the disease include natural disasters such as floods following excessive rain. This is a trend extensively recognised in most endemic areas and can provide a framework for disease, or at least outbreak, prevention. Yet shortcomings of the public health sector in such impoverished endemic areas often preclude such interventions. Similarly, implementation of protective measures to minimise exposure to infected soil and water is subject to public health sector adequacy.

The utility of doxycycline in preventing disease in susceptible populations was excellent in a study in US troops stationed in Panama [53]. Administration of doxycycline was also widely used for prophylaxis in subjects exposed during an international outbreak related to recreational activities [4]. In the latter case, however, the doxycycline benefit might actually refer to a percentage of exposed subjects who would not have developed clinical disease anyway. Other efforts to implement doxycycline prophylaxis in endemic settings have not proved as statistically significant [54,55]. At present, doxycycline administration appears a logical preventive measure upon potential exposure to leptospirosis. Moreover, it may serve preventively both for other zoonoses with a common environmental distribution and for other tropical infections that may pose risks for travellers.

Developing a human vaccine for leptospirosis would be an ideal approach, especially for populations of endemic areas. However, the road seems long: the immune response in leptospirosis has not been clarified adequately and although genome sequencing may aid in outlining immunogenic and virulence factors of the pathogen, this will take several years, since the first candidates have only recently emerged [56]. Human vaccines have been used regionally in the former Soviet Union [57], Japan [58], China [59] and Cuba [60]. Results from their use have scarcely passed to the international medical literature and doubts about the side-effect profile and the potentially short-lived protective immunity exist [7]. Furthermore, whole-cell vaccines may potentially induce autoimmunity [58].
Until scientific advances in understanding leptospirosis allow for significant advances in leptospirosis treatment, there is a clear need for better utilisation of existing antibiotics. The efficacy of either penicillin, doxycycline (in intravenous form if available) or a third-generation cephalosporin should be tested in a multinational clinical trial that will enrol patients infected by various serovars and will have strict criteria for patient inclusion. Further subgroups of different severe clinical forms could then be evaluated for antibiotic efficacy in these settings. The setting for such a co-ordinated approach exists, the obvious example being the International Leptospirosis Society. Raising public awareness of the significance, in terms of both morbidity and mortality, of the disease may allow for administrative support of such efforts. Until then, the golden rule of potential patient benefit should guide clinicians.

References


