Cytokine response in human leptospirosis with different clinical outcomes: a systematic review

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Abstract

Background: Leptospirosis is a neglected zoonotic disease which is a major challenge for clinicians and public health professionals in tropical countries. The cytokine storm during the second (immune) phase is thought to be a major contributory factor for the leptospirosis disease severity. We aim to summarize evidence for cytokine response in leptospirosis at different clinical outcomes.

Methods: A systematic review was carried out to examine the cytokine response in leptospirosis patients using relevant scientific databases. Reference lists of the selected articles were also screened. Quality of the selected studies was assessed by using the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.

Results: Of the 239 articles retrieved in the initial search, 18 studies fulfilled the selection criteria. India and Thailand have produced the highest number of studies (17% each, n = 3). The majority were comparative cross-sectional studies (72%, n = 13). Overall the quality of the selected studies was fair regardless of few drawbacks such as reporting of sample size and the lack of adjustment for confounders. Microscopic agglutination test (67% - 12/18) and enzyme-linked immunosorbent assay (50% - 9/18) were commonly used for the confirmation of leptospirosis and the measurement of cytokines respectively. IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10 and TNF-α levels were found to be significantly higher in severe than in mild leptospirosis. There were equivocal findings on the association between IL-1β, TNF-α and IL-10/TNF-α ratio and disease severity.

Conclusions: Leptospirosis had a wide-range of elevated cytokines. However, prospective studies in-relation to the onset of the symptom are required to better understand the pathophysiology of cytokine response in leptospirosis.

Keywords: Cytokines, Chemokines, MAT assay, ELISA, Severe leptospirosis, Weil’s disease

Background

Recent outbreaks of leptospirosis in different parts of the world show that the disease is re-emerging [1, 2]. The clinical picture of the disease is diverse and vary from flu-like illness to severe disease with multi-organ failure and death [3]. Clinical management of leptospirosis is always a challenge to the physicians due to the highly variable nature of its presentation. Traditionally, complications of leptospirosis are described in the second (immune) phase of the disease [3]. The most common reported causes of death in leptospirosis included respiratory, cardiac, or renal failure, and septic shock [4]. Rarely, early complications and death were attributed to the Jarisch-Herxheimer reaction [5].

The variation of disease severity is attributed to the differences in virulence factors of Leptospira [6], inoculum size [7] and the host immune response [8], especially via cytokine production. The pathogenesis of leptospirosis is
still not fully described; however, the innate immune-
mediated complications are described. Several molecules
of the infectious agents like lipopolysaccharides, hemoly-
sins, outer membrane protein and the glycolipoprotein
have been implicated with the disease [3, 9]. It is proposed
that the pathogenesis of leptospirosis is driven through
the cytokine response [10].

Many viral infections show an abnormal immune re-
response and cytokine production [11]. Dengue hemorrhagic
fever (DHF) is closely linked to the host innate and adaptive
immune response. IL-6, IL-8, IL-10, IP-10, MCP-1, TNF-α
and vascular endothelial growth factors (VEGF-A) promote
clinical manifestations of DHF [12]. Pathogenesis of Ebola
virus is influenced by multiple factors out of which exces-
sive inflammatory response is a significant feature [13]. The
potential source of inflammatory cytokines during multiple
viral hemorrhagic fever infections could vary. Dendritic
cells secrete minimal amounts of cytokines since they are
targeted by multiple viruses (arenaviruses, bunyaviruses,
filoviruses, and flaviviruses). However, monocytes and mac-
rophages appear to be playing a dominant role in secreting
inflammatory cytokines during these infections [11]. Severe
systemic clinical manifestations of gram-positive sepsis are
also attributed to the non-specific pathogen-associated mo-
lecular pattern effect of peptidoglycan and lipoteichoic acid
which trigger toll-like receptor 2 and induce inflammation.
Similarly, lipopolysaccharides has its inflammatory effect
through trigger toll-like receptor 4 [14]. The function of the
immune system is to eliminate the microbial pathogen by
producing pro-inflammatory agents such as cytokines.
However, tissue injury could be possible with excessive pro-
duction of cytokines [15]. We aim to systematically review
the previous evidence on cytokine response in leptospirosis
at different clinical outcomes.

**Methods**

**Eligibility criteria**

Full-text articles which reported cytokine response in
human leptospirosis were included in this review. Re-
ports in the non-English language were excluded. Re-
ports were not excluded based on the year of publication
or patient population.

**Information sources and search strategy**

The studies published before 31st of August 2018 were
identified through systemic searches of electronic databases
and cross-checking reference lists of the selected
articles. Cochrane-Library, Google-Scholar, Google,
PubMed, Science-Direct, Trip and Web of Science were
the databases searched using a string of keywords
(Fig. 1). Appropriate Medical Subjects Heading (MeSH)
and other relevant terms were used to identify pub-
lished studies.

**Study selection**

IS performed a comprehensive literature search. All se-
lected titles and abstracts were independently screened
by IS and DR. Full-text articles were assessed when the
abstract was unclear. The selected studies were inde-
pendently reviewed by SA to confirm eligibility.

**Data collection process, data items and data analysis**

Year of publication, demographic details, study design,
methods of leptospirosis confirmation, types and methods

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**Cochrane Library - 00, Google - 91, Google scholar - 13 and Trip search - 82**

(“Leptospira” OR “Leptospirosis” OR “Weil’s Disease”) AND (“Cytokines” OR “Chemokines”)

**PubMed - 52**

(“Leptospira” [Title/Abstract] OR “Leptospirosis” [Title/Abstract] OR “Weil Disease” [Title/Abstract]
OR “Leptospirosis” [Mesh] OR “Weil Disease” [Mesh] OR “Leptospira” [Mesh]) AND
(“Cytokines” OR “Chemokines”)

**Science Direct - 01**

TITLE-ABSTR-KEY (“Leptospira” OR “leptospirosis” or “Weil Disease”) AND TITLE-ABSTR-KEY
(“Cytokines” OR “Chemokines”)

**Web of Science - 00**

*TOPIC: (Leptospirosis) OR TOPIC: (Leptospira) OR TOPIC: (Weil’s disease) Refined by: TOPIC:
(“Cytokines” OR “Chemokines”)

**Total - 239**

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Fig. 1 Keywords for databases and the number of search results
of cytokine analysis and outcomes were extracted from the selected studies. The Population, Intervention, Comparator and Outcome (PICO) were patients with leptospirosis / severe disease / fatal outcome, cytokine analysis, healthy individuals/patients with mild disease/survivors and the cytokine levels respectively. SI units were used for presenting data. The data were analysed using Microsoft Excel (Additional file 1). Descriptive statistics were used to describe the data. The Cochrane guideline for systematic review was followed [16]. The review is presented according to the PRISMA - Preferred Reporting Items for Systematic Reviews guidelines [17]. Quality assessment of the selected studies was done using the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (Additional file 2) [18]. Graphs were drawn using the GraphPad Prism 8 software [19].

Results
Selected studies
A total of 239 search results were identified via the database search and additionally two articles were identified by screening the reference list (Fig. 2). After removal of duplicates, 177 articles were included for the title and abstract screening. Out of the above, 134 articles were excluded due to irrelevance to study objective, unavailability of full text and non-English language. The full-texts of the remaining 43 articles were examined for suitability to the review criteria, and 25 were excluded. After the screening procedure, 18 articles were selected for the systematic review [20–37]. Selected articles were published over 18 years from 2000 to 2018. Quality assessment of the selected studies revealed a lack of reporting of sample size justification (or power description or variance or effect estimates), blinding of outcome assessors to the exposure status and the statistical adjustment of potential confounding variables. Summary of the quality assessment of the selected studies is given in Additional file 2.

Characteristics of the studies
Most of the studies were conducted in India and Thailand (each 17% - 3/18). The majority of the studies were comparative cross-sectional studies (83% - 15/18). Patients with clinical suspicion (seronegative) (1/18), presumptive diagnosis (2/18), confirmed diagnosis (3/18), exposure (1/18), mild disease (7/18), severe disease
(7/18), acute kidney injury (1/18), hepatitis (2/18), scrub typhus (1/18), recovery (2/18) and fatal (1/18) were included as subjects in the selected studies. Healthy controls were used in 11 studies. The timing of the sample collection for cytokine measurement was reported in four studies, and it varied from 3 days to 2.8 years. A total of 1264 subjects participated in the selected studies. Thirteen studies reported the composition of male and female participants and accordingly there were a total of 551 males and 188 females. The mean age of the patients varied from 28.3 to 54.2 years. Microscopic agglutination test (MAT) (67% - 12/18) was commonly used for confirmation of leptospirosis. Other methods were clinical signs, culture, IFA-IgM, IgG, IgM ELISA, Lepto Tek Dri-DOT, Microscopy, nested PCR, PCR and RTPCR (Additional file 1). Enzyme-linked immunosorbent assay (ELISA) (50% - 9/18) was commonly used for the measurement of cytokines. Other methods were Bio-Plex multiplex cytokine assay (2/18), Bio-PlexTM suspension array system (1/18), Chemiluminescent enzyme immunoassay (1/18), Cytometric beads array multiplex assay (1/18), Flow cytometric analysis (2/18), Flow cytometer (FACSCalibur) inflammatory colorimetric bead array (1/18) and Protein microarray (quantitative RayBIO) (1/18) (Additional file 1).

Cytokine response in leptospirosis patients
Cytokines Eotaxin, Eotaxin-2, G-FG, G-CSF, GM-CSF, I-309, ICAM-1, IFN-γ, IL-1β, IL-1α, IL-1RA, IL-2, IL-3, IL-4, IL-5, IL-6, IL-6SR, IL-7, IL-8, IL-9, IL-10, IL-11, IL-12P40, IL-12P70, IL-12, IL-13, IL-15, IL-16, IL-17A, IL-18, IL-21, IL-23, IP-10, MCP-1, MCP-2, M-CSF, MIG, MIP-1α, MIP-1β, MIP-1δ, PDGF, PDGF-BB, RANTES, sTNFR1, sTNFR2, TGF-β, TGF-β1, TIMP-2, TNF-α, TNF-β, VEGF were studied in the selected articles (Additional file 1). TNF-α levels were measured in all studies except one.

Studies reported Eotaxin-2 [22], G-CSF [22], GM-CSF [22, 33], IFN-γ [22], IL-1β [22], IL-2 [35], IL-4 [22], IL-6 [21, 22, 26, 31, 33, 34], IL-7 [22], IL-8 [21, 23, 26, 31, 33, 36], IL-10 [21, 22, 26, 31, 36], IL-11 [22], IL-12P40 [28], IL-13 [22], IL-17 [22], IL-21 [20], IL-23 [20], IP-10 [27, 33], MCP-1 [22, 33], MIG [27], MIP-1β [22], sTNFR1 [22], TNF-α [20–22, 31, 34, 35] and VEGF [33] as elevated among leptospirosis patients. In addition, studies also reported IL-1β [21, 26], IL-12P70 [21, 26] and TNF-α [21, 23, 26, 36], levels as low or undetectable in leptospirosis patients and healthy controls. Higher levels of IL-8 [36], IL-10 [36] and lower levels of TNF-α [36] were found to be associated with better prognosis. The first, 5 days of infection showed peak levels of IL-1RA, MCP-1, MIP-1β and TNF-α; the second 5 days had peak levels of GM-CSF, IL-1β, IL-6, IL-8, IL-9, IP-10 and MIP-1α; VEGF peaked at 11–15 days [33]. Tuero et al. 2010 revealed a significantly less peripheral blood mononuclear cell production of IL10 in patients than in controls [25]. Kyriakidis et al. 2011 showed that the day of illness is a determinant of cytokine levels and that the age of the patients correlates with sTNFR1 levels [24]. An involvement of Th17 cells in the immunopathogenesis of leptospirosis was proposed by Bandara et al. 2018 because an increase in IL-17A, IL-21 and IL-23 levels were observed [20]. Latha et al. 2015 demonstrated significant levels of TNF-α and IL-6 in sera which were reactive in Leptospira tarassovi outer membrane protein IgM ELISA [34]. Wang et al. 2012 revealed that the secretion of pro-inflammatory cytokines is induced by hemolysin of Leptospira interrogans in human macrophages [22]. Table 1 summarizes mean (SD) of the five most commonly reported cytokines among leptospirosis patients with different outcomes and the controls (Fig. 3).

Cytokines response in severe leptospirosis
IL-1β [37], IL-2 [37], IL-4 [37], IL-6 [31], IL-8 [31, 37], IL-10 [31, 37] and TNF-α [35, 37] levels were significantly higher in severe than in the mild group. Elevated levels of IFN-γ [37], IL-6 [26, 37], IL-8 [26, 37], IL-10 [24, 37], sTNFR1 [24] and TNF-α [23] were observed in fatal outcomes. IL-21 and IL-23 were significantly elevated in patients with renal failure than in mild disease [20]. Leptospiral hepatitis showed a suppressed TNF-α and a 3–4 fold increase in liver enzymes along with elevated levels of IL-8 [23]. Liver insufficiency also had elevated levels of IL-23 and TNF-α [20] than in mild disease. A study revealed a significantly lower TNF-α with pulmonary disease [33] while another study had higher TNF-α levels in pulmonary disease [24]. Patients with severe pulmonary haemorrhage had significantly higher levels of IL-5, IL-6, IL-8, and IL-10. IL-6 was associated with severe pulmonary haemorrhage in fatal outcomes even after adjusting for age and duration of symptoms [37].

High IL-10/TNF-α ratio was associated with leptospirosis [36] and fatal outcomes [37]. By contrast, other studies showed that low IL-10/TNF-α ratio was associated with leptospirosis [35], severe disease [32] and fatal outcomes [24]. However, IL-10/TNF-α ratio did not correlate with sex or age [24].

Cytokines response in leptospirosis treatment
More than five doses of antimicrobial agents (penicillin, ceftriaxone, doxycycline) significantly lowered IL-6 and IL-8 levels, when compared to lower doses. IL-8 levels were negatively associated with the total number of antimicrobial doses administered (penicillin, ceftriaxone, doxycycline) and also with the number of ceftriaxone doses administered [21]. Extended sustained low-efficiency dialysis via hemodiafiltration significantly decreased the post-admission levels of IL-17, IL-7, and MCP-1 compared to the dialysis...
| Study No | Year | Type | Control | Leptospirosis patients | Mild disease | Severe disease | Survived | Fatal | Liver involvement | Renal involvement |
|----------|------|------|---------|------------------------|-------------|---------------|----------|-------|------------------|------------------|
| Bandara K | 2018 | IL-10 | 12 | 18.6 (10.5) | 307 (33.2) | NR | NR | 7 | 11.4 (9.4) | 14 |
| | | TNF-α | 12 | 63.0 (37.2) | 700.0 (6190) | NR | NR | 7 | 422.5 (373.1) | 14 |
| Fernando N | 2018 | IL-6 | 18 | 0.1 (0.2) | 394 (83.1) | 26 | 57.9 (87.7) | 25 | 12.8 (13.5) | NR |
| | | IL-8 | 18 | 0.1 | 51 (35.2) | 26 | 36.2 (35.7) | 25 | 17.7 (16.2) | NR |
| | | IL-10 | 18 | 0.0 | 51 (68.7) | 26 | 48.0 (78.1) | 25 | 0.9 (1.8) | NR |
| Chirathaworn C | 2016 | IL-6 | 25 | 2.7 | NR | NR | 20 | 224.5 (11.0) | NR |
| | | IL-8 | 25 | 32.5 | NR | NR | 20 | 1024.0 (11.0) | NR |
| | | IL-10 | 25 | 4.0 | NR | NR | 20 | 234.7 (11.0) | NR |
| | | TNF-α | 25 | 7.9 | NR | NR | 20 | 30.7 (11.0) | NR |
| Papa A | 2015 | IFN-γ | 20 | 137.1 | NR | NR | 7 | 170.4 (11.0) | NR |
| | | IL-6 | 20 | 10.2 | NR | NR | 7 | 190.8 (11.0) | NR |
| | | IL-8 | 20 | 19.2 | NR | NR | 7 | 223.6 (11.0) | NR |
| | | IL-10 | 20 | 20.4 | NR | NR | 7 | 43.4 (11.0) | NR |
| | | TNF-α | 20 | 55.2 | NR | NR | 7 | 124.5 (11.0) | NR |
| Rizvi M | 2014 | IL-8 | 30 | 53.8 | NR | NR | 46 | 1760 (11.0) | NR |
| | | IL-10 | 30 | 12.8 | NR | NR | 46 | 329 (11.0) | NR |
| | | TNF-α | 30 | 167.0 | NR | NR | 46 | 465 (11.0) | NR |
| Kyriakidis I | 2011 | IL-6 | 30 | 46.2 | NR | NR | 39 | 442 (5.9) | NR |
| | | IL-8 | 30 | 68 | NR | NR | 39 | 55 (5.5) | NR |
| | | IL-10 | 30 | 47.3 | NR | NR | 39 | 199 (5.5) | NR |
| | | TNF-α | 30 | 799 | NR | NR | 39 | 1034 (5.5) | NR |

N Total, NR Not reported, SD Standard deviation
via hemodialysis among patients with acute kidney injury or acute respiratory distress syndrome following leptospirosis [30].

**Discussion**

The review had data from studies which included leptospirosis patients with varying degree of severity. Although, the review produced valuable data on the possible role of cytokines in leptospirosis disease severity, there were equivocal findings with regards to IL-1β, TNF-α and IL-10/TNF-α ratio among the selected studies. Failure to measure soluble TNF receptor-1 (sTNFR1) might have led to low levels of TNF-α in some studies, as the bound TNF-α will not be included in the analysis [37]. IL-1β, IL-6 and TNF-α were proposed to be pro-inflammatory cytokines which enhance the inflammatory response in leptospirosis [10]. However, the present review found IL-1β to be low among leptospirosis patients, IL-6 to be elevated and TNF-α to be equivocal. The above findings could be due to the variation in the time of sample collection in relation to the onset of the symptoms. Nevertheless, results among the complicated leptospirosis showed elevated levels of IL-6 and TNF-α which shows a higher degree of pro-inflammatory action. In contrast, IL-10 is thought to be the most important anti-inflammatory cytokine which restores the immunological homeostasis in leptospirosis [10]. In addition, IL-4 and IL-13 restrict the inflammatory response [10]. The present review revealed elevated levels of the above-mentioned anti-inflammatory cytokines among leptospirosis patients and patients with complicated disease. The findings suggest that anti-inflammatory response is also expected to increase in complicated leptospirosis. Therefore, a low IL-10 / TNF-α is most probable among patients with complicated disease.

Differential diagnosis for leptospirosis includes DHF, chikungunya, hanta virus and malaria infections. Similar to the present review, IL-6 [38], IL-8 [38], IL-10 [38, 39], IP-10 [38], MCP-1 [38], TNF-α [40, 41] and VEGF [39]...
were found to be elevated in DHF, a condition common to almost all endemic settings for leptospirosis. IL-6, IL-12, IL-1RA, IP-10, and MCP-1 were also found to be elevated in chikungunya [42–44]. Hanta virus infection, a disease which can mimic pulmonary leptospirosis, had shown elevation of GM-CSF, IL-2, IL-6, IL-10, IL-12P40, IL-17 and VEGF [45]. Fatal outcomes from *Patho-
moldium falciparum* malaria showed elevated levels of IL-6, IL-10 and TNF-α than in survival which was comparable to the results on leptospirosis [46]. Cerebral malaria was found to have high levels of TNF-α in fatal outcomes [46]. Moreover, Ebola viral infection showed elevation of pro-inflammatory cytokines IL-6 and IL-8 in non-survivors similar to the present review [47, 48]. It is interesting to note that IL-6 was found to be elevated in leptospirosis, DHF, chikungunya, hanta virus, malaria and Ebola infections. However, cytokine response alone cannot be used to differentiate the above conditions.

Both Papa et al. [33] and Kyriakidis et al. [24] showed that the day of illness is a determinant of cytokine levels. The above fact emphasizes the need of cytokine selection in relation to the day of illness, if we are to use the cytokine levels for disease monitoring. The selected studies were heterogeneous, and the methods used for the diagnosis of leptospirosis and measurement of cytokines varied between studies, making it impossible for proper evidence synthesis. Although, the quality assessment revealed few drawbacks such as reporting of sample size and the lack of adjustment for confounders, overall the quality was fair. Nevertheless, the review points out the importance of clinical assessment as the cytokine response in leptospirosis is still poorly understood, and published literature are highly inadequate to produce a clear picture.

**Conclusions**

A wide-range of cytokines were found in the circulation during a leptospirosis infection. Especially, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10 and TNF-α levels were significantly higher in severe disease. However, prospective studies with minimal sampling bias, standard diagnosis and optimum cytokine measurement in-relation to the onset of the symptom are required to better understand the pathophysiology of cytokine response in leptospirosis.

**Supplementary information**

Supplementary information accompanies this paper at https://doi.org/10.1186/s12879-020-04998-9.

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