

# Why Are Children With Bronchiolitis At Risk Of Urinary Tract Infections?

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**Abstract:** Viral respiratory infections are frequently eliminated from human bodies without any sequelae. Secondary serious bacterial infection (SBI) in children with acute bronchiolitis has been an apprehension expressed by health care providers. Several published studies have shown an association between acute bronchiolitis and secondary bacterial infection, including urinary tract infections (UTI). However, the proposed mechanism by which a virus can induce UTIs is not yet known. The aim of this commentary is to update the current evidence of risk of UTI in children with bronchiolitis. We present several clinical studies related to the topic as well as a brief review of the potential pathophysiology of secondary infections that could present with viral respiratory illness.

**Keywords:** bronchiolitis, infection, urine

## Review Of The Literature

Viral respiratory infections are frequently eliminated from human bodies without any sequelae. Nevertheless, in some occasions viruses can evade the immune reaction of the airways, leading to austere respiratory diseases.<sup>1</sup> Potent mechanical and immunosuppressive methods protect the lungs against external infections, but a solitary respiratory tract infection can change immunity and pathology.<sup>2</sup> Secondary serious bacterial infection (SBI) in children with acute bronchiolitis has been an apprehension expressed by health care providers.<sup>3</sup> Several published studies have shown an association between acute bronchiolitis and secondary bacterial infection, including urinary tract infections (UTI).<sup>4-13</sup> However, the proposed mechanism by which a virus can induce UTIs is not yet known.

In a review of the literature, the percentage of patients with fever with positive urine cultures ranged from 4.2% to 20.0% in infants <3 months of age and 0% to 7.4% in older children (3 to 36 months of age).<sup>14</sup> Ralston et al<sup>3</sup> conducted a systematic review delineating the risk of occult SBI in young febrile infants presenting with either “clinical bronchiolitis” or “proven RSV infection”. The review included 11 studies.<sup>4-7,9-13,15,16</sup> The rate of urinary tract infections in the 11 studies analyzed was 3.3% (95% confidence interval, 1.9–5.7%). The authors concluded the rate of urine cultures positive for bacteria was noteworthy, though asymptomatic bacteriuria may have muddled the results. Recently, McDaniel et al<sup>17</sup> conducted a systematic review and meta-analysis exploring the prevalence of UTI in infants and young children with bronchiolitis when positive urinalysis (UA) results being incorporated into the UTI definition. The investigators included 18 studies,<sup>4-7,9,11-13,15,16,18-25</sup> seven of which had UA information.<sup>4,11,16,18,20-22</sup> The definition of positive UA varied among the studies. Some considered positive UA as

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having more than 5 white blood cells per high-powered field, while others considered the UA positive by having bacteriuria, positive leukocyte esterase, or positive nitrite. The prevalence of UTI in bronchiolitis in the 18 studies was 3.1% (95% CI, 1.8–4.6%). The authors further analyzed the data of the 7 studies where the presence of pyuria or nitrites was a diagnostic criterion to define UTI and the prevalence of UTI was 0.8% (95% CI, 0.3–1.4%).

However, the above studies did not sub-categorize the prevalence of UTI in bronchiolitis per specific respiratory virus as a trigger. Hendaus et al<sup>8</sup> studied the prevalence of urinary tract infection in infants and children with bronchiolitis. The study included 835 pediatric patients with acute bronchiolitis. The mean ( $\pm$ SD) age at diagnosis was 3.47 $\pm$ 2.99 months. There were 325 (39%) girls and 510 (61%) boys. Participants were divided into three groups: group 1 comprised of children hospitalized with bronchiolitis and a positive diagnosis for respiratory syncytial virus (RSV) bronchiolitis; group 2 comprised of children hospitalized with clinical bronchiolitis with no virus detected; and group 3 comprised of children hospitalized with clinical with bronchiolitis and a positive diagnosis respiratory virus other than RSV. After applying inclusion and exclusion criteria, RSV was notorious in 352 (45.7%) patients; respiratory viruses other than RSV were identified in 275 (35.7%) patients and 142 (18.4%) were studied but had no viruses detected. Non-RSV viruses comprised of rhinovirus (n=85 [31%]), parainfluenza virus type 4 (n=40 [14%]), adenovirus (n=40 [14%]), human metapneumovirus (HMPV) (n=27 [10%]), bocavirus (n=27 [10%]), coronavirus (n=20 [7%]), parainfluenza virus (hPIV) type 1 (n=9 [3.4%]), hPIV type 2 (n=9 [3.4%]), hPIV type 3 (n=9 [3.4%]), and H1N1pdm09 (n=9 [3.4%]). The definition of UTI was adopted from the American Academy of Pediatrics as

clinicians should require both urinalysis results that suggest infection (pyuria and/or bacteriuria) and the presence of  $\geq 50,000$  colony-forming units (CFUs) per milliliter of a uropathogen cultured from a urine specimen obtained through catheterization or suprapubic aspirate.<sup>26</sup>

The overall prevalence of UTI was 10%, and was most common in group 3 (13.4%) trailed by group 2 (9.7%), and was least common in group 1 (6%) ( $P=0.030$ ). The most reasonable explanation of why the rate of UTI was higher in the study conducted by Hendaus et al<sup>8</sup> was because it was the first published study that sub-

categorized the prevalence of UTI in bronchiolitis per specific respiratory virus as a trigger.

## So What Could Be The Potential Pathophysiology?

The epithelium is usually protected by a layer of mucus that functions as a border.<sup>27–29</sup> Viruses can inflict impairment on host epithelial cells, and mammalian cells are susceptible to bacterial attachment during a viral sickness.<sup>30</sup> Moreover, viruses can incapacitate the mucociliary clearance arrangement, causing increased attachment of bacteria to mucins and colonization.<sup>31</sup> Viruses like the influenza and RSV might injure ciliated cells, causing ciliostasis, and hence worsening of mucociliary clearance.<sup>30,32,33</sup> Furthermore, virus-induced cell demise weakens the mechanical elimination of the close pathogens and exhibits new receptors for bacterial adherence.<sup>34</sup> The respiratory virus-infected epithelia enable the attraction of inflammatory cells, including natural killer cells, neutrophils, macrophages, and eosinophils from the bloodstream into the infected area.<sup>35</sup>

The epithelium identifies microorganisms through pattern recognition receptors, such as nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs), retinoic acid-inducible gene (RIG)-like helicases,<sup>36,37</sup> and Toll-like receptors (TLRs).<sup>29</sup> NLRs and RIG-like helicases activate innate immune reactions through cytosolic detection of viral and bacterial components,<sup>37,38</sup> while TLRs are single, noncatalytic, membrane-spanning receptor proteins utilized by the innate immune system.<sup>39</sup> Post-viral continued desensitization of lung sentinel cells to TLR signals might contribute to secondary bacterial infection. For instance, TLR4 and TLR5 pathways are modified after influenza virus infection, leading to decreased neutrophil attraction, hence resulting in increased attachment of bacteria.<sup>38</sup>

Several epithelial cells can also express the classical antiviral interferons (INFs), especially IFN- $\alpha$  and IFN- $\beta$ .<sup>40,41</sup> The link between host cells and microorganisms during sickness prompts immune reaction that comprise the generation of pro-inflammatory molecules. In spite of their important role as a bactericidal, pro-inflammatory cytokines such as TNF- $\alpha$  produced in response to infection could be injurious to the host cells.<sup>42</sup> Viruses can also have an impact in modulating many molecules such as intercellular adhesion molecule 1 (ICAM-1), carcinoembryonic antigen-related cellular adhesion 1 (CEACAM-1), and platelet-activating factor receptor (PAF-r),<sup>43</sup> resulting in a risk of bacterial adherence.<sup>44</sup>

Throughout a viral episode, TLR and RIG-I-like receptor activation prompts fabrication of type I IFNs, which can then boost the inflammatory response to TLR ligands including lipopolysaccharide (LPS).<sup>45,46</sup> Interface between type I IFNs and Nod1/Nod2 signalling results in bacterial recognition, and causes damaging effects in the virally infected host.<sup>47</sup>

## Conclusions And Recommendations

1. Published studies do not robustly support the idea that viral bronchiolitis can lead to bacterial UTI.
2. Despite the fact that a viral infection can lead to secondary bacterial infection, the mechanism of acquiring UTI after viral bronchiolitis is not very well known.
3. Large randomized studies are required to tackle the possible causation/association (bronchiolitis vs UTI).
4. Performing urine microscopy and urine culture on a febrile young child with bronchiolitis should be individualized per patient's condition.

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## Disclosure

The author reports no conflicts of interest in this work.

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