Journal of Infection 79 (2019) 389–399

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Letters to the Editor

## Elevated lactate levels in the cerebrospinal fluid associated with bacterial meningitis

*Dear Editor,*

We read with interest the recent article by Heemskerk et al. in this Journal who identified higher lactate levels in the cerebrospinal fluid (CSF) as an independent variable strongly associated with TB meningitis.[1] Here we report on a retrospective analysis of the biochemical markers, including lactate, in CSF samples collected from 2167 patients admitted between 2014–2018 with symptoms and signs of infective meningitis or encephalitis. 1364 specimens were collected from adult patients (>16 years old) and 803 from paediatric patients (<16 years old). Of the 803 paediatric patients 38 were <4 weeks old and 112 were under the age of 1 year.

Although clinical guidelines advocate the use of cerebrospinal fluid (CSF) biochemical biomarkers such as protein and glucose levels to aid diagnosis of an infective cause,[2–4] only 325 samples (15% of patients in the cohort) had all three parameters (protein, glucose and lactate) measured. 85% of the CSF samples had received at least one biochemistry result; 82% had received CSF protein measurement, 80% had received CSF glucose measurement and 16% had received CSF lactate measurement, as summarized in Table 1. 10.1% of all specimens had a positive bacterial result, whereas 5.0% of all specimens had a positive virological diagnosis, differentiated in Fig. 1A. Only one of the CSF samples analysed had a confirmed diagnosis of Mycobaterium tuberculosis, determined by culture, however no CSF lactate was provided for that sample.

In this study cohort, a lymphocytic CSF was only present in 69% of specimens with positive viral PCR whereas 92% of infections with *S. pneumoniae* or *N. meningitis* were assoicated with a raised polymorph count. Polymorphs were only raised in 22% of infections with other bacteria, confirming that a polymorphic CSF may be useful in identifying patients with *N. meningitidis* or *S. pneumoniae* infections. Interestingly, 815 patients (~40% of the total study cohort) had no confirmatory diagnosis on testing for viral and bacterial organisms despite being lymphocytic on microscopic examination. It is possible that some central nervous system infections may be caused by uncommon or not routinely tested pathogens e.g. measles, influenza A & B and RSV.[5] An alternative aetiology such as inflammation or autoimmunity may also explain this observation. Previous studies have demonstrated the complex, non-infectious aetiologies associated with meningitis and encephalitis.[6]

Protein measurement in CSF displayed the greatest range from 0.07 to 14.6 mmol/L (median 0.5 mmol/L), however elevated protein levels were not necessarily indicative of a positive bacterial or viral cause.

The levels of lactate were also variable, ranging from 0.6 and 13.3 mmol/L (median 1.5 mmol/L). UK national guidelines suggest a lactate measurement of 3.8 mmol/L or 35 mg/dL as a potential upper limit of normal.[2] To define threshold values for interpretation of what qualifies as "raised" CSF lactate, the entire cohort was examined and a 95% threshold was set at 2.4 mmol/L and this data is shown in Fig. 1B. Only 1% of the study cohort had lactate measurements greater than 3.8 mmol/L, and of these 83% (10/12) were patients infected with *N. meningitidis* or *S. pneumoniae*, while the remaining 17% (2/12) had no final diagnosis.

To ensure that CSF lactate levels were not influenced by host cells present in the specimens, Spearman's rank correlation analysis was performed comparing white blood cell count (WBC) and numbers of red blood cells (RBC) present in CSF specimens, and their possible impact on CSF lactate levels. A weak correlation was observed between levels of WBC in CSF and both protein ($R = 0.4$ $p = 0.001$) or glucose ($R = 0.17$ $p = 0.001$) but there was no significant correlation between the numbers of WBC or RBC with CSF lactate levels.

The proportion of patients with confirmed viral infection and confirmed bacterial infection which had either slightly raised (>2.4 mmol/L) or significantly raised (>3.8 mmol/L) CSF lactate levels was evaluated. Proportionally 60% of bacterial infections were associated with a CSF lactate level above 2.4 mmol/L in contrast to 17% of viral infections. The specificity for viral causes of meningitis using a cut-off value of <2.4 mmol/L was 94% (CI 95% 92–96) while the specificity of CSF lactate levels >2.4 mmol/L for bacterial infection was 79% (CI 95% 75–83), further suggesting a raised lactate level above 2.4 mmol/L may be a useful excluder of viral aetiology. Lactate levels above 3.8 mmol/L showed a high specificity for *N. meningitides* and *S. pneumoniae* of 94% (CI 95% 93–94), greater than had been described previously in published guidelines.[2] These organisms appeared to cause a marked rise in measured CSF lactate levels, with patients recorded with an average of 13.1 mmol/L (*N. meningitidis*) and 13 mmol/L (*S. pneumoniae*) (Fig. 1b).

Therefore, CSF lactate may be a useful aid to clinicians where traditional indicators of viral infection are unclear, as there was no evidence of significantly raised lactate in cases of aseptic meningitis investigated here. CSF lactate was not influenced by the number of red and white blood cells present, making it a promising biochemical tool in the event cell count is confounded where lumbar puncture results in a bloody CSF specimen. Furthermore, where limited CSF is available for study such as from neonates, biochemical analysis that includes lactate should be encouraged to aid exclusion of viral aetiology and early antibiotic escalation if necessary.

https://doi.org/10.1016/j.jinf.2019.06.004
0163-4453/© 2019 The British Infection Association. Published by Elsevier Ltd. All rights reserved.

**Table 1**
Summary of all study data subdivided by microscopy and biochemical investigations on 2167 CSF samples collected from 2014–2018. CSF samples positive for either *S. pneumoniae* and *N. meningitidis* and infections are separated as a sub-category to highlight the differences in biochemical measurements observed in these patients. Denominators are shown in brackets for each column.

| | Virology positive ($n=109$) | Virology negative ($n=2058$) | Bacteriology positive ($n=226$) | Bacteriology negative ($n=1941$) | *S. pneumoniae* or *N. Meningitidis* ($n=25$) |
|---|---|---|---|---|---|
| Raised Lymphocytes (>5 cells) | 75 (69%) | 916 (92%) | 103 (46%) | 888 (89%) | 10 (40%) |
| Raised Polypmorphs (>5 cells) | 39 (36%) | 303 (88%) | 50 (22%) | 292 (85%) | 23 (92%) |
| With all biochemistry parameters measured (%) | 12 (11%) | 149 (15%) | 32 (14%) | 149 (15%) | 16 (64%) |
| CSF Lactate measured (%) | 12 (11%) | 149 (15%) | 36 (16%) | 149 (15%) | 6 (24%) |
| CSF Protein measured (%) | 90 (82%) | 813 (82%) | 188 (83%) | 823 (83%) | 10 (40%) |
| CSF Glucose measured (%) | 97 (85%) | 793 (80%) | 190 (84%) | 793 (80%) | 10 (40%) |
| CSF Protein (>0.4 g/L) | 43 (40%) | 447 (55%) | 79 (42%) | 427 (52%) | 10 (100%) |
| CSF Glucose (<2.6 mmol/L) | 41 (38%) | 16 (2%) | 180 (95%) | 24 (3%) | 0 (0%) |
| CSF Lactate (>3.8 mmol/L) | 0 (0%) | 2 (1.4%) | 1 (2%) | 2 (1.4%) | 10 (100%) |
| CSF Lactate (>2.4 mmol/L) | 2 (17%) | 4 (3%) | 22 (60%) | 3 (2%) | 10 (100%) |

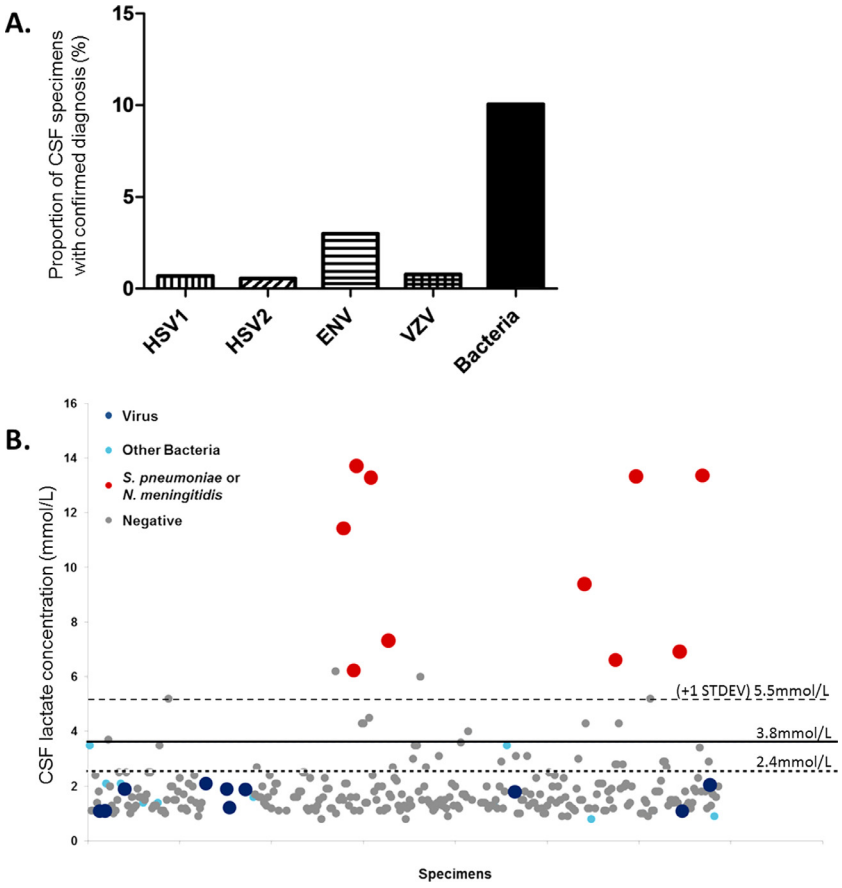


**Fig. 1.** (A) The proportion of CSF specimens with a laboratory confirmed identification of infectious organisms either Herpes simplex virus 1 (HSV1), Herpes simplex virus 2 (HSV2), Enteroviruses (ENV), Varicella zosta virus (VZV) or bacterial causes, including *Enterococcus* sp., Group A or B *Streptococcus* sp., *Escherichia* sp., *S. pneumoniae* or *N. meninigitidis*. (B) CSF lactate level measurements in CSF samples. 95% of CSF had lactate levels under 2.4 mmol/L (dotted line), with all cases of *S. pneumoniae* and *N. meningitidis greater* than CSF lactate levels greater than 1 SD above the previously published 3.8 mmol/L cut-off (solid line), and greater than 2 SD above the 2.4 mmol/L cut-off, significantly different from other bacterial or viral organisms detected.

This study suggests that the measurement of lactate is beneficial in the identification of the most dangerous bacterial causes of CNS infection, and should be considered for routine use as an early biochemical warning marker that would trigger a significant escalation of patient care. The data presented in this study provides evidence to support the use of elevated CSF lactate as a marker of meningitis caused by infection with *Neisseria meningitidis* or *Streptococcous pneumoniae* and is a valuable aid to early diagnosis before specific microbiological or virological testing results become available.

## Conflicts of interest

The authors declare that there are no conflicts of interest.

## References

1. Heemskerk A.D., Donovan J., Dang An Thu D., Thi Minh Ha D., Thi Hong Chau T., Van Vinh Chau N., et al. Improving the diagnosis of tuberculous meningitis: a prospective, international multi-centre comparison of conventional and modified Ziehl–Neelsen stain, genxpert and culture of cerebrospinal fluid. *J Infect* 2018;**77**:509–15.

2. McGill F., Heyderman R.S., Michael B., Defres S., Beeching N.J., Borrow R., et al. The UK joint specialist societies guideline on the diagnosis and management of acute meningitis and meningococcal sepsis in immunocompetent adults. *J Infect* 2016;**72**(4):405–38.
3. Griffiths M.J., McGill F., Solomon T.. Management of acute meningitis. *CME Infect Dis* 2018;**18**:164–9.
4. El Bashir H., Laundy M., Booy R.. Diagnosis and treatment of bacterial meningitis. *Arch Dis Child* 2003;**88**(7):615.
5. McGill F., Griffiths M.J., Bonnett L.J., Maria Geretti A., Michael B.D., Beeching N.J., et al. Incidence, aetiology, and sequelae of viral meningitis in UK adults: a multicentre prospective observational cohort study. *Lancet Infect Dis* 2018;**18**(9):992–1003.
6. Ambrose E., Granerod J., Clewley J.P., Davies N.W., Keir G., Cunningham R., et al. Diagnostic strategy used to establish etiologies of encephalitis in a prospective cohort of patients in england. *J Clin Microbiol.* 2011;**49**(10):3576–83.

Andrew Bosworth
*Clinical Microbiology and Public Health Laboratory, Public Health England, University Hospitals Birmingham NHS Foundation Trust, Birmingham, West Midlands B9 5SS, UK*
*Health Protection Research Unit in Emerging and Zoonotic Infections, National Institute for Health Research, UK*

Khiranmai Bhatt
*Clinical Microbiology and Public Health Laboratory, Public Health England, University Hospitals Birmingham NHS Foundation Trust, Birmingham, West Midlands B9 5SS, UK*

Alexandra Nance
*Department of Biochemistry, Division of Pathology and Laboratory Medicine, University Hospitals Birmingham NHS Foundation Trust, Birmingham, West Midlands, UK*

Gemma Winzor, Sowsan F. Atabani*
*Clinical Microbiology and Public Health Laboratory, Public Health England, University Hospitals Birmingham NHS Foundation Trust, Birmingham, West Midlands B9 5SS, UK*

*Corresponding author.
*E-mail address:* sowsan.atabani@phe.gov.uk

Accepted 8 June 2019
Available online 13 June 2019

https://doi.org/10.1016/j.jinf.2019.06.004

© 2019 The British Infection Association. Published by Elsevier Ltd. All rights reserved.

## Clinical and virological characteristics of human infections with H7N9 avian influenza virus in Shenzhen, China, 2013–2017

*Dear Editor,*

Recent articles in this Journal have reported the human infections with highly pathogenic (HP) H7N9 avian influenza virus (AIV) in Shenzhen city of China, and compared the clinical and virological characteristics of human infection with HP-H7N9 and low pathogenic (LP) H7N9 viruses.[1,2] Shenzhen is an international port city located at the Pearl River delta region and on the East Asian-Australian migration flyway. It provides an ideal environment for the emergence and circulation of novel influenza viruses with potential cross-species transmission due to the unique ecosystem, presence of live poultry markets (LPMs) and Cantonese dietary habits.[3] During the five waves of human H7N9 infections in 2013–2017, 45 human cases have been hospitalized in Shenzhen. Here we further summarized and analyzed the clinical and virological characteristics of human H7N9 infections in Shenzhen during 2013–2017.

The cases were reported only in Waves 2, 3 and 5 (Fig. S1(A)), with case numbers of 24, 13 and 8, respectively. Cases in each wave were reported during November to May, and peaked in January (Fig. S1(A)), which is similar with the overall temporal distribution of human cases during the five waves.[4] Meanwhile, the cases were mainly from Longgang (15), Futian (7), Luohu (10), Baoan (5) and Longhua (4) districts, and there were cases in Longgang, Futian and Baoan districts across the three waves (Fig. S1(B)). The median age of patients was 53 years, ranging from 6 to 82 years, and 28.9% of the patients were 60 years of age or older (Table 1). Although majority of LPMs were shut down after governmental intervention, visiting LPMs (53.3%) still served as the main cause of poultry exposure for the H7N9 cases in Shenzhen (Table 1), which may result from the lasting sporadic and small-scale live poultry trading. Most of the cases (73.3%) had co-existing chronic medical conditions, which has been shown to be a high risk factor for H7N9 infection and death.[5] As a result, almost all the cases showed severe respiratory disease with a high prevalence of multiple organ dysfunction syndrome (MODS) (Table 1). *A. baumannii* co-infection was frequent (42.4%) in the cases, which was shown to be associated with dysfunctions of immune responses in H7N9 patients.[6] Therefore, prevention and control of *A. baumannii* infections should be a focus during H7N9 treatment, especially when invasive mechanical ventilation is used.[6] Consistent with previous studies, the acute phase of the cases was accompanied with a number of significantly elevated cytokines (Fig. S2), among which IL-2, MIG, MCP-1, IP-10 and MIF have been found to be associated with the disease severity of H7N9 infection.[7] Of note, the expression profiles of some cytokines were different in H7N9 cases from different waves (Fig. S2), which may be associated with the co-existing chronic medical conditions or bacterial co-infections.

The overall CFR in Shenzhen was about 13.3% (Table 1), far lower than the nationwide CFR during the five waves of human H7N9 infections (39.6%).[4] This may be attributed to several comprehensive measures including reasonable use of neuraminidase inhibitors, mechanical ventilation, corticosteroid, antibiotics, fluid infusion, and the strict prevention and control of nosocomial infection. The proportions of human cases receiving mechanical ventilation (71.1%) and corticosteroid (84.4%) treatment were higher than the overall human H7N9 infections.[5] Studies have shown that corticosteroids could downregulate proinflammatory cytokine transcription and subsequently inhibit the cytokine storm, while use of high-dose corticosteroids has been shown to be associated with an increase in mortality and significantly longer durations of viral shedding in H7N9 infected patients.[8] During our treatment, we took a strategy of short-term use of small dose corticosteroid at the earlier course of H7N9 infection. Despite successful use in our patients, however, the accurate role of low dose corticosteroids for patients with severe influenza needs further validation. Furthermore, nearly half of the patients (42.2%) received antivirals before admission, which may also contribute to the lower CFR of H7N9 patients in Shenzhen.

Phylogenetic analyses of the HA and NA genes of H7N9 isolates in Shenzhen showed that the isolates in Waves 2 and 3 belonged to the Pearl River Delta lineage, and isolates in the same wave were clustered together with high homology (Fig. 1). While during Wave 5, 90% (9/10) of the HA genes and 70% (7/10) of NA genes belonged to the Yangtze River Delta lineage, in which the HA and NA genes were clustered in different subclade and showed

**Table 1**
Characteristics on subjects hospitalized with infection of H7N9 AIV in Shenzhen, 2013–2017.

| Characteristics | Wave 2, $N=24$ | Wave 3, $N=13$ | Wave 5, $N=8$ | All, ($N=45$) |
|---|---|---|---|---|
| **Median age (range)** | 54 (31–82) | 52 (6–77) | 52.5 (33–81) | 53 (6–82) |
| **Age subgroups** | | | | |
| 0–15 years | 0 (0%) | 1 (7.7%) | 0 (0%) | 1 (2.2%) |
| 16–59 years | 16 (66.7%) | 9 (69.2%) | 6 (75%) | 31 (68.9%) |
| ≥60 years | 8 (33.3%) | 3 (23.1%) | 2 (25%) | 13 (28.9%) |
| **Male** | 14/24 (58.3%) | 9/13 (69.2%) | 5/8 (62.5%) | 28/45 (62.2%) |
| **Poultry exposure** | 17/24 (70.8%) | 11/13 (84.6%) | 4/8 (50%) | 32/45 (71.1%) |
| Visited live poultry market | 13/24 (54.2%) | 8/13 (61.5%) | 3/8 (37.5%) | 24/45 (53.3%) |
| Exposure to backyard poultry | 0/24 (0%) | 0/13 (0%) | 1/8 (12.5%) | 1/45 (2.2%) |
| Exposure to sick/dead poultry | 0/24 (0%) | 0/13 (0%) | 1/8 (12.5%) | 1/45 (2.2%) |
| Occupational exposure | 2/24 (8.3%) | 2/13 (15.4%) | 0/8 (0%) | 4/45 (8.9%) |
| **Co-existing chronic medical conditions** | 18/24 (75%) | 9/13 (69.2%) | 6/8 (75%) | 33/45 (73.3%) |
| Chronic heart disease | 8/24 (33.3%) | 6/13 (46.2%) | 1/8 (12.5%) | 15/45 (33.3%) |
| Chronic lung disease | 3/24 (12.5%) | 1/13 (7.7%) | 1/8 (12.5%) | 5/45 (11.1%) |
| Chronic renal disease | 2/24 (8.3%) | 0/13 (0%) | 0/8 (0%) | 2/45 (4.4%) |
| Chronic liver disease | 1/24 (4.2%) | 3/13 (23.1%) | 3/8 (37.5%) | 7/45 (15.6%) |
| Diabetes | 5/24 (20.8%) | 1/13 (7.7%) | 1/8 (12.5%) | 7/45 (15.6%) |
| Cancer | 0/24 (0%) | 0/13 (0%) | 0/8 (0%) | 0/45 (0%) |
| **Bacterial co-infections** | 13/24 (54.2%) | 12/13 (92.3%) | 8/8 (100%) | 33/45 (73.3%) |
| Acinetobacter baumannii | 8/13 (61.5%) | 3/12 (25%) | 3/8 (37.5%) | 14/33 (42.4%) |
| **Interval, median days (IQR)**[+] | | | | |
| Onset to admission | 7 (6, 9) | 6 (3, 9) | 7 (6.75, 8.25) | 7 (6, 9) |
| Onset to starting antiviral treatment | 6 (6, 8.25) | 6 (3, 6) | 6.5 (5.5, 7.25) | 6 (5, 8) |
| Onset to laboratory confirmation | 7 (5.75, 10) | 7 (5, 8) | 8 (7, 8.25) | 7 (6, 9) |
| **Complications** | | | | |
| Pneumonia | 24/24 (100%) | 12/13 (92.3%) | 8/8 (100%) | 44/45 (97.8%) |
| ARDS | 21/24 (87.5%) | 8/13 (69.2%) | 8/8 (100%) | 37/45 (82.2%) |
| Severe ARDS | 11/24 (45.8%) | 6/13 (46.1%) | 6/8 (75%) | 23/45 (51.1%) |
| Respiratory failure | 21/24 (87.5%) | 8/13 (69.2%) | 8/8 (100%) | 37/45 (82.2%) |
| Hepatic insufficiency | 14/24 (58.3%) | 6/13 (46.2%) | 5/8 (62.5%) | 25/45 (55.6%) |
| Renal insufficiency | 5/24 (20.8%) | 3/13 (23.1%) | 3/8 (37.5%) | 11/45 (24.4%) |
| Cardiac failure | 2/24 (8.3%) | 5/13 (38.5%) | 2/8 (25%) | 9/45 (20%) |
| Shock | 3/24 (12.5%) | 2/13 (15.4%) | 3/8 (37.5%) | 7/45 (15.6%) |
| **Treatment** | | | | |
| Received antivirals ≤ 2 days after illness onset | 1/24 (4.2%) | 1/13 (7.7%) | 0/8 (0%) | 2/45 (4.4%) |
| Received antivirals 3–5 days after illness onset | 4/24 (16.7%) | 5/13 (38.5%) | 2/8 (25%) | 11/45 (24.4%) |
| Received antivirals ≥ 6 days after illness onset | 19/24 (79.1%) | 7/13 (53.8%) | 6/8 (75%) | 32/45 (71.2%) |
| Received antivirals before admission | 8/24 (33.3%) | 7/13 (53.8%) | 4/8 (50%) | 19/45 (42.2%) |
| Corticosteroid | 21/24 (87.5%) | 9/13 (69.2%) | 8/8 (100%) | 38/45 (84.4%) |
| Mechanical ventilation | 18/24 (75%) | 6/13 (46.2%) | 8/8 (100%) | 32/45 (71.1%) |
| **Case fatality rate** | 2/24 (8.3%) | 1/13 (7.7%) | 3/8 (37.5%) | 6/45 (13.3%) |

the highest homology with different isolates from Dongguan City (Fig. S2). The results indicated that the genetic diversity became higher in Wave 5, which was found to be an underlying reason for the sharp increases in the number of human infections during Wave 5.[4] Moreover, there were some differences in the molecular characterizations of H7N9 viruses in Shenzhen from different waves. For example, several key substitutions associated with increased virulence/transmissibility in mammals and NA inhibitor-resistance were found in most of the isolates from all waves (Table S1), while some specific substitutions which may influence the pathogenesis of H7N9 virus were only found in isolates from Wave 5, such as the K526R and A588V substitutions. Furthermore, consistent with previous studies,[2,4] higher prevalence of neuraminidase inhibitor-resistance mutation (R292K) was found in isolates from Wave 5, which highlighted the importance of real-time monitoring of the emergence of R292K mutation methods during treatment.[9]

In summary, our study provides insights into the outbreaks and treatment of human H7N9 infections in Shenzhen. Active surveillance of H7N9 virus, interventions on poultry trading and vaccination of poultry have prevented and eliminated the 'sixth wave' of human H7N9 infections in China during 2018.[10] However, researchers also found that H7N9 virus still circulates in live poultry, and the host range has expanded to ducks,[10] which suggests that the public threat of H7N9 virus still exists. It is therefore important to conduct continuous precautionary measures and surveillance of H7N9 and other AIVs in the future.

## Declaration of Competing Interest

The authors have declared that no conflicts of interest exist.

## Funding

This work was supported by the National Science and Technology Major Project under Grant [number 2018ZX10711001, 2017ZX10204401, 2017ZX10305501]; Shenzhen Science and Technology Research and Development Project under Grant [number JCYJ20180504165549581, JCYJ20170413141236903], China Postdoctoral Science Foundation under grant [number 2018M641508], Sanming Project of Medicine in Shenzhen under grant [number SZSM201412003, SZSM201512005].

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jinf.2019.07.010.

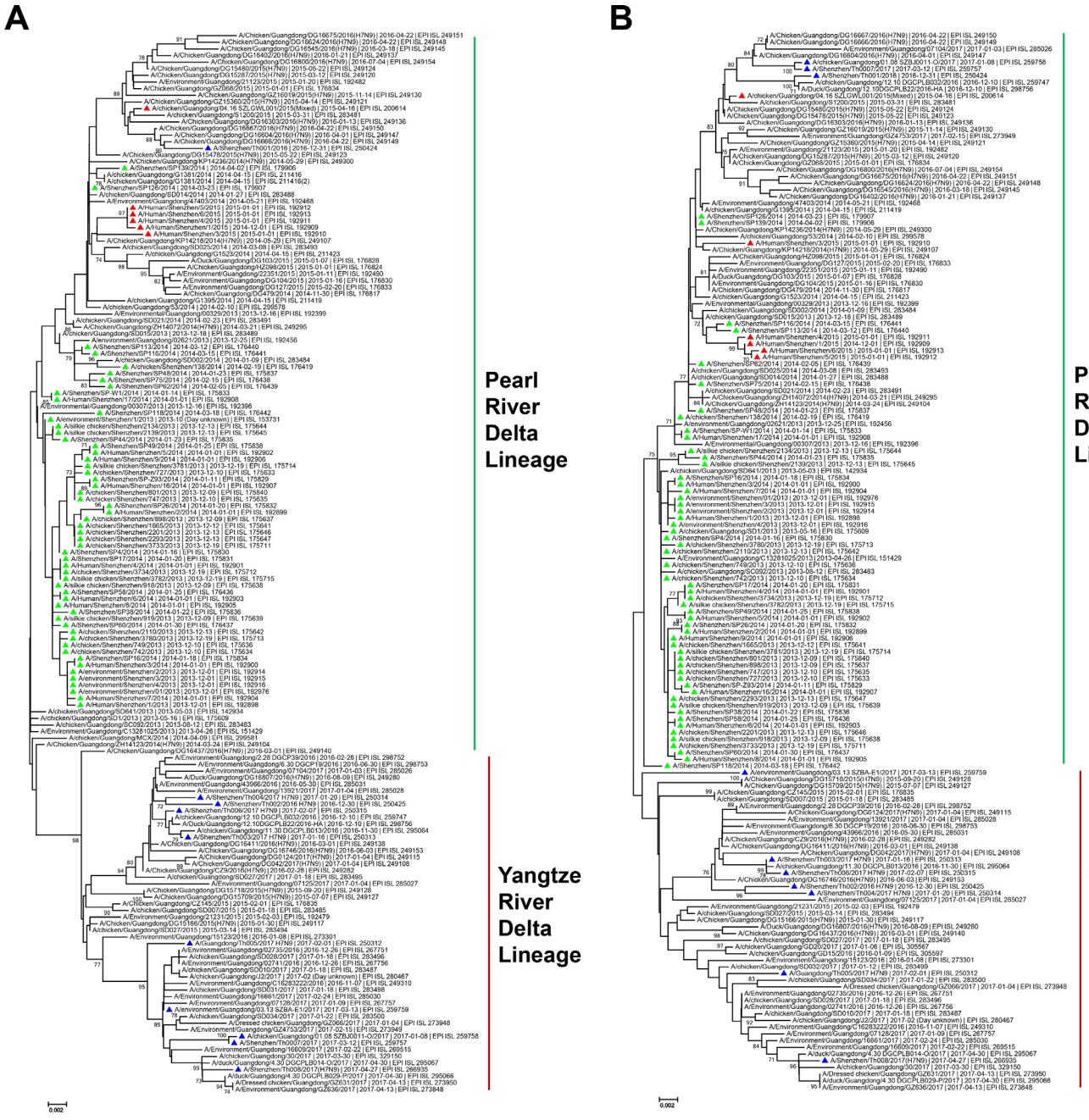


**Fig. 1.** *Phylogenetic analysis of the HA and NA genes of H7N9 viruses in Shenzhen.* Panel A and B show the phylogenetic trees of available HA and NA genes of H7N9 viruses from Shenzhen and LPMs in other areas of Guangdong province during the five waves of human H7N9 infections in the Genbank and GISAID databases. H7N9 isolates from Shenzhen in Wave 2, 3 and 5 were labeled with green, red and blue triangles, respectively.

## References


1. Yang Y., Wong G., Yang L., Tan S., Li J., Bai B., et al. Comparison between human infections caused by highly and low pathogenic H7N9 avian influenza viruses in wave five: clinical and virological findings. *J Infect* 2019;**78**(3):241–8.
2. Zhang F., Bi Y., Wang J., Wong G., Shi W., Hu F., et al. Human infections with recently-emerging highly pathogenic H7N9 avian influenza virus in China. *J Infect* 2017;**75**(1):71–5.
3. Gilbert M., Golding N., Zhou H., Wint G.R., Robinson T.P., Tatem A.J., et al. Predicting the risk of avian influenza a H7N9 infection in live-poultry markets across Asia. *Nat Commun* 2014;**5**:4116.
4. Quan C., Shi W., Yang Y., Yang Y., Liu X., Xu W., et al. New threats from H7N9 influenza virus: spread and evolution of high- and low-pathogenicity variants with high genomic diversity in wave five. *J Virol* 2018;**92**(11), pii: e00301-18.
5. Wang X., Jiang H., Wu P., Uyeki T.M., Feng L., Lai S., et al. Epidemiology of avian influenza a H7N9 virus in human beings across five epidemics in mainland China, 2013–17: an epidemiological study of laboratory-confirmed case series. *Lancet Infect Dis* 2017;**17**(8):822–32.
6. Liu W.J., Zou R., Hu Y., Zhao M., Quan C., Tan S., et al. Clinical, immunological and bacteriological characteristics of H7N9 patients nosocomially co-infected by acinetobacter Baumannii: a case control study. *BMC Infect Dis* 2018;**18**(1):664.
7. Guo X.J., Thomas P.G.. New fronts emerge in the influenza cytokine storm. *Semin Immunopathol* 2017;**39**(5):541–50.
8. Cao B., Gao H., Zhou B., Deng X., Hu C., Deng C., et al. Adjuvant corticosteroid treatment in adults with influenza a (H7N9) viral pneumonia. *Crit Care Med* 2016;**44**(6):e318–28.
9. Yang Y., Li S., Wong G., Ma S., Xu Z., Zhao X., et al. Development of a quadruple qRT-PCR assay for simultaneous identification of highly and low pathogenic H7N9 avian influenza viruses and characterization against oseltamivir resistance. *BMC Infect Dis* 2018;**18**(1):406.
10. Shi J., Deng G., Ma S., Zeng X., Yin X., Li M., et al. Rapid evolution of H7N9 highly pathogenic viruses that emerged in China in 2017. *Cell Host Microbe* 2018;**24**(4):558–68.e7.

Yang Yang[1], Chenguang Shen[1]
*Shenzhen Key Laboratory of Pathogen and Immunity, State Key Discipline of Infectious Disease, Shenzhen Third People's Hospital, Second Hospital Affiliated to Southern University of Science and Technology, Shenzhen 518112, China*
*CAS Key Laboratory of Pathogenic Microbiology and Immunology, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Disease, Institute of Microbiology, Center for Influenza Research and Early-warning (CASCIRE), Chinese Academy of Sciences, Beijing 100101, China*

Jin Li[1]
*School of Public Health (Shenzhen), Sun Yat-sen University, Shenzhen 518107, China*

Rongrong Zou
*Shenzhen Key Laboratory of Pathogen and Immunity, State Key Discipline of Infectious Disease, Shenzhen Third People's Hospital, Second Hospital Affiliated to Southern University of Science and Technology, Shenzhen 518112, China*

Gary Wong
*Institut Pasteur of Shanghai, Chinese Academy of Sciences, Shanghai 200031, China*
*Département de Microbiologie-Infectiologie et d'immunologie, Université Laval, Québec City G1V 0A6, Canada*

Ling Peng, Liuqing Yang
*Shenzhen Key Laboratory of Pathogen and Immunity, State Key Discipline of Infectious Disease, Shenzhen Third People's Hospital, Second Hospital Affiliated to Southern University of Science and Technology, Shenzhen 518112, China*

Shisong Fang
*Shenzhen Center for Disease Control and Prevention, Shenzhen, 518055, China*

Jianming Li, Xiaohe Li, Weibo Wu, Xiao Jiang, Lijiao Zeng, Jianfeng Lan
*Shenzhen Key Laboratory of Pathogen and Immunity, State Key Discipline of Infectious Disease, Shenzhen Third People's Hospital, Second Hospital Affiliated to Southern University of Science and Technology, Shenzhen 518112, China*

Yuhai Bi
*Shenzhen Key Laboratory of Pathogen and Immunity, State Key Discipline of Infectious Disease, Shenzhen Third People's Hospital, Second Hospital Affiliated to Southern University of Science and Technology, Shenzhen 518112, China*
*CAS Key Laboratory of Pathogenic Microbiology and Immunology, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Disease, Institute of Microbiology, Center for Influenza Research and Early-warning (CASCIRE), Chinese Academy of Sciences, Beijing 100101, China*

George F. Gao
*Shenzhen Key Laboratory of Pathogen and Immunity, State Key Discipline of Infectious Disease, Shenzhen Third People's Hospital, Second Hospital Affiliated to Southern University of Science and Technology, Shenzhen 518112, China*
*CAS Key Laboratory of Pathogenic Microbiology and Immunology, Collaborative Innovation Center for Diagnosis and Treatment of Infectious Disease, Institute of Microbiology, Center for Influenza Research and Early-warning (CASCIRE), Chinese Academy of Sciences, Beijing 100101, China*
*University of Chinese Academy of Sciences Medical School, Chinese Academy of Sciences, Beijing 101408, China*

Jing Yuan*
*Shenzhen Key Laboratory of Pathogen and Immunity, State Key Discipline of Infectious Disease, Shenzhen Third People's Hospital, Second Hospital Affiliated to Southern University of Science and Technology, Shenzhen 518112, China*

Yingxia Liu**
*Shenzhen Key Laboratory of Pathogen and Immunity, State Key Discipline of Infectious Disease, Shenzhen Third People's Hospital, Second Hospital Affiliated to Southern University of Science and Technology, Shenzhen 518112, China*
*University of Chinese Academy of Sciences Medical School, Chinese Academy of Sciences, Beijing 101408, China*

*Corresponding author.
**Corresponding author at: Shenzhen Key Laboratory of Pathogen and Immunity, State Key Discipline of Infectious Disease, Shenzhen Third People's Hospital, Second Hospital Affiliated to Southern University of Science and Technology, Shenzhen 518112, China.
*E-mail addresses:* 13500054798@139.com, yingxialiu@hotmail.com

[1] These authors contributed equally to this study.

Accepted 25 July 2019
Available online 30 July 2019

https://doi.org/10.1016/j.jinf.2019.07.010

© 2019 The British Infection Association. Published by Elsevier Ltd. All rights reserved.

## Urine catheterization of elderly hospitalized patients unable to provide a urine sample for culture

*Dear Editor,*

Recently reported in this journal was that certain accepted signs and symptoms of a urinary tract infection (UTI) have limited value[1]. This should influence how to define a symptomatic UTI when consensus opinion recommends a urinary catheterization procedure in elderly febrile patients if they cannot provide a urine specimen.[2,3] However, although there can be clinical utility of urine cultures to direct appropriate antibiotic therapy, the decision to catheterize should consider the risk of an indwelling urine catheter during hospitalization and at discharge.[4,5]

We prospectively identified all catheterized patients aged 65 years or more in a single internal medicine department who had a Foley urinary catheter inserted to obtain a urine specimen for culture. The attending physician decided on the removal the catheter on admission. We excluded all patients with other indications for placement of a urethral catheter[4] and recorded age, sex, disability (needs help or bedridden), whether the patient had an extra-urinary cause for hospitalization (Table 1) and urine volumes when catheterized on admission as reported previously.(Table 2)[5]

Patients discharged were followed-up for 24 months by chart review of subsequent hospitalizations and by contacting the patients' family or medical staff if follow-up was less than one month. Outcome variables included the presence of a urethral catheter on discharge and follow-up, hospitalizations for a possible urinary tract infection, renal failure, and mortality. All deaths with an initial urine volume ≥500 mL were reviewed.

**Table 1**
Presentation of patients catheterized to obtain a urine sample for culture.

| Presentation | N | % |
|---|---|---|
| Possible urinary tract infection | 118 | 41.0 |
| Fever[a] | 77 | 26.7 |
| Nonspecific symptoms[b] | 30 | 10.4 |
| Urinary tract symptoms[c] | 11 | 3.8 |
| Extra-urinary tract presentation | 170 | 59.0 |
| Respiratory tract infection | 74 | 25.7 |
| Cerebral vascular accident | 24 | 8.3 |
| Ischemic heart disease/congestive heart failure | 21 | 7.3 |
| Syncope | 16 | 5.6 |
| Laboratory abnormalities | 14 | 4.9 |
| Decubitus ulcer/cellulitis | 8 | 2.8 |
| Gastroenteritis/constipation | 8 | 2.8 |
| Trauma | 5 | 1.7 |
| Total | 288 | 100 |

[a] >37.5 °C or <36 °C.
[b] deterioration, lethargy, mental status changes.
[c] dysuria, increased frequency, macroscopic hematuria, new incontinence, costovertebral pain or tenderness to palpation).

Cultures were processed using standard microbiologic methods, and isolates were identified by the VITEK 2 system (bioMérieux, Marcy l'Etoile, France). Bacteriuria was defined as the presence of at least $10^5$ colony-forming units per milliliter. We calculated means, standard deviations, and proportions with 95% confidence intervals (95% CI). To predict a urethral catheter on follow-up, we used a logistic regression model, and retained only variables that significantly added to the model ($p < 0.05$) and the area under the curve was calculated. We received approval from the hospital ethics committee (0029–16 LND).

There were 398 urine cultures in 420 patients with urine volumes measured at the time of a new insertion of a urine catheter on admission. We excluded patients admitted with urinary tract obstruction ($N = 26$), the need for urine output monitoring ($N = 40$), end stage cancer for comfort ($N = 9$), decubitus ulcers ($N = 10$), macroscopic hematuria ($N = 6$), worsening renal function with a creatinine ≥3 mg/dL ($N = 18$), and one patient with a pelvic fracture.

The remaining 288 patients were aged 84 ± 8 years, 32.3% were males ($n = 93$), and most were disabled (35.8% ($N = 103$) needs help, 47.2% ($N = 136$) bedridden). There were 170 patients (59.0%, 95% CI −53.1%–64.8%) with extra-urinary tract reasons for admission (Table 1) and urine cultures were positive in 35.3% (60/170) of them compared to 58.5% (69/118) of the other patients ($p < 0.001$).

There were 32 patients (11.1%, 95% CI −7.5%–14.7%) discharged with a urethral catheter; 24 patients with urine volumes ≥500 mL. In the remaining eight patients with a urine catheter on discharge, six patients had symptomatic urinary retention after removal of the catheter and two had no apparent reason.

There was no follow-up in 14.2% of the patients (41/288), without a detectable selection bias (comparison of predictor variables). During 14.4 ± 8.8 month's follow-up, the risk for an indwelling catheter increased as urine volumes increased, but there was no association with subsequent hospitalizations for bacteriuria without an extra-urinary cause, nor with mortality (Table 2). In patients with urine volumes of ≥500 mL, there were 23 deaths in 71 patients on follow-up not significantly different from those with lower urine volumes (Table 2). There were two deaths from urosepsis, one in a patient with an indwelling urethral catheter. The other patient was without a urine catheter, had subsequent urine volumes <150 mL, and recurrent hospitalizations for urinary tract infections. The other deaths were unrelated to urine volumes or indwelling catheters. On logistic regression analysis, there were increased odds for a follow-up indwelling catheter if discharged with a urethral catheter (odds ratio 5.43, 95% CI 2.11–14.0) after adjustment for the urine volume groups (odds ratio 1.49, 95% CI 1.11–2.0). No other variables added significantly to the model. The area under the curve was 74.8%.

The major finding in this study is that in elderly hospitalized patients unable to provide a urine sample for culture, the catheterization procedure resulted in an 11% risk for a urethral catheter at discharge, that increased the odds of having an indwelling catheter on follow-up by over 5-fold. An incidental finding of an elevated urine volume on catheterization was common, and was associated with the use of an indwelling urethral catheter, but not with other morbidity or mortality suggesting that the catheter can be safely removed in those patients.

Our study has limitations. The physician behavior might affect the proportion of patients catheterized to obtain a urine specimen (influenced by various definitions of what constitutes a symptomatic UTI that are not evidence based[1], the type of catheter used, and the risk of discharge with a urethral catheter and on follow-up. Efforts to remove a urethral catheter are likely to vary in the hospital and on follow-up. In our setting, the Foley catheter is introduced in the emergency department, and the patient is admitted with the catheter, removed at the discretion of the attending physician. In emergency departments where an in and out straight catheter is used to obtain a urine sample, it is unclear if straight catheters will cause less trauma and in those with a high urine volume whether a Foley catheter will then be introduced. Further studies in other settings are warranted.

Consensus opinion recommends a urinary catheterization procedure in elderly febrile patients with a possible UTI who cannot provide a urine specimen.[2,3] Our results suggests the decision should take into consideration the risk of indwelling catheters after the procedure. There may be patients where those adverse consequences outweighs the benefits of antibiotic therapy directed by in-vitro bacterial sensitivities.

## Conflict of interest

The authors have no conflicts of interest.

## Acknowledgments

The study was not funded.

**Table 2**
The association of urine volumes on admission with urethral catheters at discharge, and catheters, UTI hospitalizations and mortality on follow-up.

| Urine volume | All patients | Discharge catheter | Patients with follow-up | | | |
|---|---|---|---|---|---|---|
| (mL) | N (%) | N (%) | N (%) | Catheter | UTI hospitalization | Mortality |
| <150 | 121 (42.0) | 4 (3.3) | 107 (43.3) | 10 (9.3) | 21 (19.4) | 44 (41.1) |
| 150–299 | 40 (13.9) | 0 (0.0) | 36 (14.6) | 4 (11.1) | 8 (22.2) | 17 (47.2) |
| 300–499 | 41 (14.2) | 4 (9.8) | 33 (13.4) | 3 (9.1) | 7 (21.2) | 10 (30.3) |
| ≥500 | 86 (29.9) | 24 (27.9) | 71 (28.8) | 24 (33.8) | 18 (25.4) | 23 (32.4) |
| *p* value | | <0.001 | | <0.001 | 0.842 | 0.319 |
| Total | 288 | 32 (11.1) | 247 | 41 (16.6) | 54 (21.9) | 94 (38.1) |

## References

1. Gbinigie O.A., Ordóñez-Mena J.M., Fanshawe T.R., Plüddemann A., Heneghan C.. Diagnostic value of symptoms and signs for identifying urinary tract infection in older adult outpatients: systematic review and meta-analysis. *J Infect* 2018;**77**:379–90.
2. High K.P., Bradley S.F., Gravenstein S., Mehr D.R., Quagliarello V.J., Richards C., et al. Clinical practice guideline for the evaluation of fever and infection in older adult residents of long-term care facilities: 2008 update by the infectious diseases society of america. *Clin Infect Dis* 2009;**57**:375–94.
3. Meddings J., Saint S., Fowler K.E., Gaies E., Hickner A., Krein S.L., et al. The ann arbor criteria for appropriate urinary catheter use in hospitalized medical patients: results obtained by using the rand/UCLA appropriateness method. *Ann Intern Med* 2015;**162**(9):S1–34 Suppl.
4. Shimoni Z., Rodrig J., Kamma N., Froom P.. Will more restrictive indications decrease rates of urinary catheterization? An historical comparative study. *BMJ Open* 2012;**2**(2):e000473 Mar 8. doi:10.1136/bmjopen-2011-000473.
5. Shimoni Z., Avdiaev R., Froom P.. Urine cultures in hospitalized geriatric patients presenting with fever. *Am J Med Sci* 2017;**353**:17–21.



Zvi Shimoni
*Department of Internal Medicine B, Laniado Hospital, Netanya, Israel*
*Ruth and Bruce Rappaport School of Medicine, Haifa, Israel*

Strilets Evgeniy
*Department of Internal Medicine B, Laniado Hospital, Netanya, Israel*

Paul Froom*
*Clinical Utility Unit, Sanz Medical Center, Laniado Hospital, Netanya, Israel*
*School of Public Health, University of Tel Aviv, Israel*

*Corresponding author at: Department of Clinical Utility, Laniado Hospital, Netanya, Israel.
*E-mail addresses:* zshimoni@laniado.org.il, strilets08@mail.ru, froomp@gmail.com



Accepted 3 August 2019
Available online 14 August 2019

https://doi.org/10.1016/j.jinf.2019.08.002


© 2019 The British Infection Association. Published by Elsevier Ltd. All rights reserved.

## Urinary antigen tests and the investigation of suspected community acquired pneumonia

*Dear Editor,*

We read with interest the study published in February 2017 by O' Connor et al., (Rapid urinary antigen testing for the investigation of bacteraemic respiratory pneumococcal disease; underutilised and undervalued?) suggesting the promotion of urinary antigen tests (UATs) in pneumonia.[1] Community acquired pneumonia (CAP) remains a significant cause of mortality worldwide and accurate, timely detection of the causative agent significantly impacts patient progress.[2] The primary bacterial cause of CAP is *Streptococcus pneumoniae* (SP), accounting for an estimated 27.3%.[3] *Legionella pneumophila* (LP) most commonly causes Legionnaire's Disease; a life-threatening pulmonary infection of increasing incidence requiring specific treatment; potentially causing hospital and community outbreaks, minimised by rapid, accurate detection.[4]

Culture-based techniques and sputum culture likely underdiagnose Pneumococcal CAP e.g. Only ~25% of patients have a bacteraemia. Specific culture-based techniques for *Legionella* spp. report variable sensitivity (20 – 80%).[3,4] Whilst culture-based methods have advantages e.g. antibiotic susceptibility, a rapid test with high sensitivity and specificity would enhance diagnostic and antimicrobial stewardship.

UATs for SP are the most widely used indirect diagnostic test with varying sensitivity (77 – 88%) and specificity (67 – 100%)[5] however, in children, a positive result may indicate carriage. LP UATs have reported sensitivity of 70% and specificity of 90 – 95%, but only test for *Legionella* serotype 1, missing ~15% of cases. In both UATs, false positives occur in polymicrobial infections and may be negative in early infection in patients without bacteraemia and can degrade with time between sampling and testing.[4,5]

SP and LP UATs are recommended in specific circumstances by European, American and British guidelines on the management of CAP.[6,7] However, consensus is lacking between these guidelines on whom to test and when.[7] As a result, we investigated the appropriateness and clinical utility of SP and LP UATs for suspected CAP in a 'real-life' cohort.

We conducted a retrospective, cross-sectional cohort study in five hospitals serving a population of 3 million in East London. All UATs for all patients in all clinical areas submitted between December 2014-January 2015 (P1) and December 2015-January 2016 (P2) were reviewed. UATs were requested by the treating clinical team and were tested using CE-marked BinaxNOW® *S. pneumoniae* and *L. pneumophila* UATs, in an ISO-15,189 accredited laboratory.

Medical records and microbiology results were interrogated for all cases and clinical and microbiological metadata was collected, including demographics, indication for testing, presence of consolidation on Chest X-Ray (CXR) and whether there was an escalation/de-escalation in antimicrobials (choice of narrower/broader spectrum antibiotic or change in route of administration) as a result or a request for an HIV test. Appropriateness of antigen testing was determined using criteria including the CURB65 score (moderate/severe) and presence/absence of consolidation on chest radiography (CXR), as described by the British Thoracic Society (BTS) and National Institute for Clinical Excellence (NICE) CAP guidelines.

Within the two-year period, 596 patients were tested. In P1, 329 patients were tested and in P2, 267 patients had UATs culminating in a final sample size of 987 unique tests (Fig. 1). In P1 and P2, 51% and 56% of patients were male, aged between 3 – 101 (median: 62) and 1 – 91 (median: 61). Based on testing, quality assurance and overheads, the total cost for this four-month period was £25,712.

In P1 11/329 (3.3%) patients and in P2 5/267 (1.9%) had positive SP UATs. There were no positive LP UATs in either period. Of the 16 patients with positive SP UATs, 4 (25%) had *S. pneumoniae* isolated from either blood/sputum culture and of these, 2 (50%) individuals had this result available before the UATs were sent. 12 of 16 patients (75%) had consolidation on CXR and 5/16 patients (31%) with a positive test did not meet either BTS or NICE guideline criteria for testing. None of the positive antigen tests affected management i.e. No change in antibiotic choice, route, or a new HIV test.

A sub-group of the 596 patients had their CXRs independently reported randomly as part of the 2014 BTS CAP audit. Consolidation was present in 24.4% of the 217 patients (36.4% of all patients) whose CXRs were independently reviewed.

All 987 tests were scored according to the BTS and NICE guidelines for CURB65 score and presence of consolidation on CXR and were deemed appropriate in 25% (246) of cases. The most common reasons for inappropriate testing were inappropriate clinical information provided and no evidence of consolidation on CXR, and respiratory failure secondary to a non-infectious cause.

We believe this is the first large 'real-life' cohort study undertaken rather than a focussed study on a well-defined subpopulation. Despite almost 1000 tests in 587 patients, there were no positive LP UATs and only 12 positive SP UATs, in whom 25% had the organism isolated elsewhere. Consolidation was present in only a quarter of patients in whom testing was requested and only

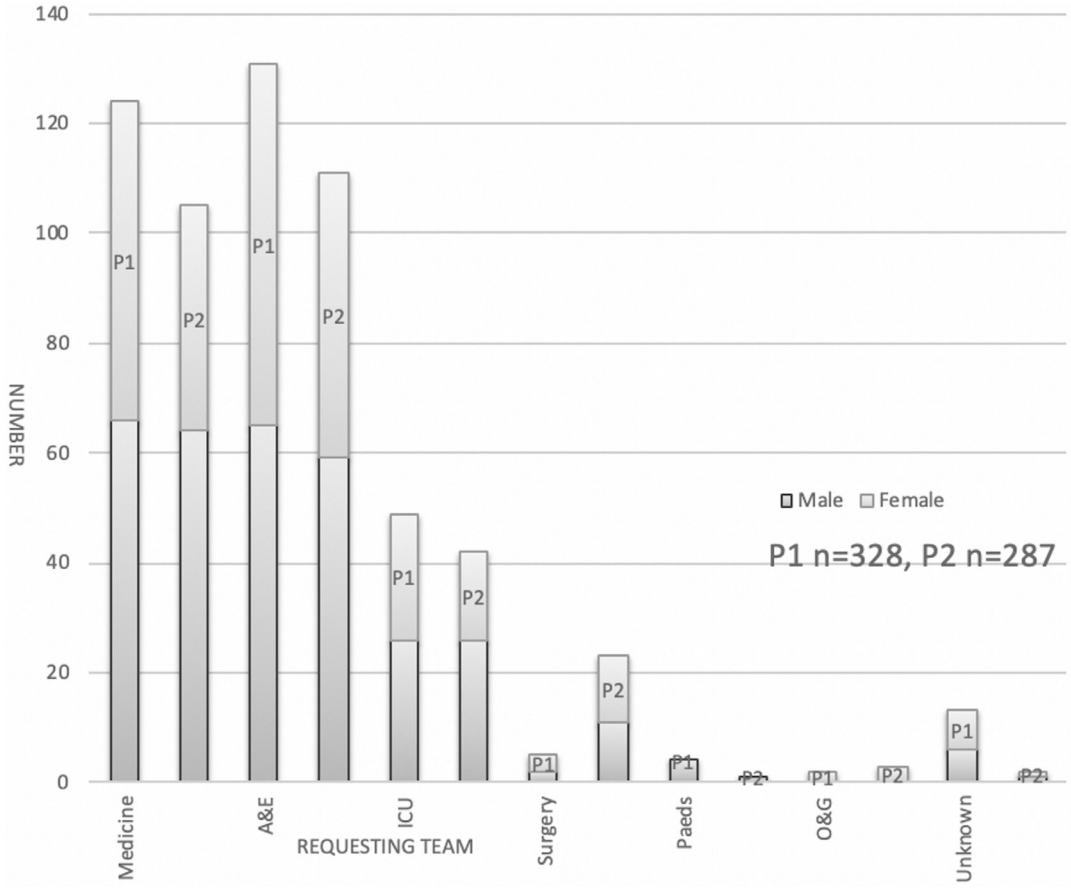


**Fig. 1.** Study population and origin of tests in Phase 1 (P1) and Phase 2 (P2).

25% (246/987 tests) were deemed appropriate (NICE/CURB65 criteria). None of the positive SP UATs directly led to a change in antimicrobials, route of administration, or HIV test.

Our study has strengths and limitations. We included all patients of all ages in whom pneumonia was suspected (not confirmed), regardless of co-morbidity in contrast to studies where only patients >18 in well-defined populations were included.[8,9] However, our study had a moderate sample size, data collection was restricted to two, two-month periods during the winter, giving potential seasonal bias, and there were no positive LP UATs. Ideally, all 596 CXRs would be independently reviewed and specific study populations selected in detail. By reviewing all tests, we could provide a realistic cohort study of testing within the UK, including populations where tests may not be positive e.g. patients with HIV/immunosuppressed/children.

This study raises questions and potential options for future management. Simple diagnostic stewardship, e.g. requesting that UATs are discussed with Infectious Diseases, Respiratory or Microbiology colleagues to indicate which patients are tested may be useful. However, recent studies show recommended indications for UATs have poor sensitivity/specificity for identifying patients with positive UATs.[9] Alternatively, re-directing resources for active case finding via respiratory pathogen multiplex PCR tests may identify hidden disease and be more cost-effective.[2,10]

UATs were costly (>£75,000 p.a.), rarely positive and, when positive, did not lead to change in patient management. Further studies should consider whether novel strategic diagnostic stewardship or active case finding via PCR may improve diagnosis and cost-efficiency.

## Declaration of Competing Interest

We declare no competing interests and received no funding for this study.

## References

1. O'Connor C., O'Hara F., McCarthy C., Morgan R., Humphreys H.. Rapid urinary antigen testing for the investigation of bacteraemic respiratory pneumococcal disease; underutilised and undervalued? *J Infect* 2017;**74**(2):198–200.
2. Salez N., Vabret A., Leruez-Ville M., Andreoletti L., Carrat F., Renois F., et al. Evaluation of four commercial multiplex molecular tests for the diagnosis of acute respiratory infections. *PLoS One* 2015;**10**(6). doi:10.1371/journal.pone.0130378.
3. Said M.A., Johnson H.L., Nonyane B.A.S., Deloria-Knoll M., OBrien K.L.. Estimating the burden of pneumococcal pneumonia among adults: a systematic review and meta-analysis of diagnostic techniques. *PLoS One* 2013;**8**(4).
4. Sharma L., Losier A., Tolbert T., Dela Cruz C.S., Marion C.R.. Atypical pneumonia: updates on legionella, chlamydophila, and mycoplasma pneumonia. *Clin Chest Med* 2017;**38**(1):45–58.
5. Blaschke A.J.. Interpreting assays for the detection of streptococcus pneumoniae. *Clin Infect Dis* 2011;**52**(SUPPL. 4).
6. Griffith D.E., Aksamit T., Brown-Elliott B.A., Catanzaro A., Daley C., Gordin F., et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med* 2007;**175**(4):367–416.
7. Lim W.S., Smith D.L., Wise M.P., Welham S.A.. British thoracic society community acquired pneumonia guideline and the NICE pneumonia guideline: how they fit together. *BMJ Open Respir Res* 2015;**2**(1):1–3.
8. Marcos M.A., Jiménez de Anta M.T., de la Bellacasa J.P., González J., Martínez E., García E., et al. Rapid urinary antigen test for diagnosis of pneumococcal community-acquired pneumonia in adults. *Eur Respir J* 2003;**21**(2):209–14.
9. Bellew S., Grijalva C.G., Williams D.J., Anderson E.J., Wunderink R.G., Zhu Y., et al. Pneumococcal and legionella urinary antigen tests in community-acquired pneumonia: prospective evaluation of indications for testing. *Clin Infect Dis* 2019;**68**(12):2026–33.

10. Priest P.C., Slow S., Chambers S.T., Cameron C.M., Balm M.N., Beale M.W., et al. The burden of legionnaires' disease in New Zealand (LegiNZ): a national surveillance study. *Lancet Infect Dis* 2019;**19**(7):770–7.

Sakib Rokadiya*
*Department of Medicine, Imperial College London, United Kingdom*

Poppy Denniston, William Ricketts
*Department of Respiratory Medicine, Barts Health NHS Trust, London, United Kingdom*

Jonathan Lambourne
*Department of Infection, Barts Health NHS Trust, London, United Kingdom*

*Corresponding author.
*E-mail addresses:* Sakib.Rokadiya@nhs.net, William.Ricketts@bartshealth.nhs.uk, Jonathan.Lambourne@bartshealth.nhs.uk

Accepted 18 August 2019
Available online 20 August 2019

https://doi.org/10.1016/j.jinf.2019.08.013

© 2019 The British Infection Association. Published by Elsevier Ltd. All rights reserved.

## Correlation of the lymphocyte: Monocyte ratio amongst polymerase chain reaction confirmed cases of influenza infections

*Dear Editor,*

Recently in a systemic review and meta-analysis published in the Journal of Infection, Rusell et al., described the utility of the peripheral lymphocyte-to-monocyte ratio (LMR) in respiratory viral infections.[1,3] Based on this study, a LMR <2 shows good predictive value for respiratory virus infection, especially influenza.

We describe a series of 15 cases of polymerase chain reaction (PCR)-proven influenza-infected hospitalized adult patients based on throat swab specimens over the course of two months. Their biochemical markers, including the neutrophil-to-lymphocyte ratio (NLR) and LMR, coinciding with the time of collection of the respiratory specimen, are described in Table 1.

Amongst these 15 patients, only patient 12 has a diagnosis of another concomitant infection (infective endocarditis, for which the patient was already receiving antimicrobial treatment at time of influenza diagnosis). Patient 6 developed a concomitant myocardial infarction and demised during the same admission. All the other patients were discharged well, from the hospital. 13/15 (86.7%) patients received treatment with oseltamivir. Within this patient cohort, 80.0% has a LMR of <2 and 93.3% has a LMR <2.5 based on the peripheral cell count at the point of influenza diagnosis. Other biomarkers such as procalcitonin and C-reactive protein, as shown in our cohort, are also seen to be significantly elevated in some cases. For instance, only 75.0% of the cases, with a measured procalcitonin, have a level of ≤0.49 ug/L.

Lower respiratory tract infections, remain a leading cause of mortality and morbidity worldwide, with the influenza virus known to be one of the top four high-burden aetiologies.[2] Misguided usage of antibiotics in viral pneumonias, contributing to antibiotic resistance is a real-world problem. Low described this as “doubly misguided”, since antibiotics have no effect on treating viral infections and its prescription exerts selection pressure on bacteria colonizing treated individuals, thereby contributing to antimicrobial resistance. Early identification of influenza infections have implications on appropriate antiviral use, as well as avoiding unnecessary antibiotics.

PCR-based tests remain the most sensitive means of diagnosing influenza infections but are limited largely by its costs and lack of availability in certain parts of the world. In contrast, the full blood count is cheap, frequently performed, and hence readily available. As concluded by Rusell et al., the LMR is a potentially useful tool in identifying patients with influenza infection amongst individuals presenting with respiratory tract infections. Our cohort of 15 patients, albeit small, supports the use of the LMR in predicting influenza respiratory infections. However, the optimal cut-off point remains unknown, given that using a cut-off of <2 would potentially miss 20.0% of our cases. On the other hand, increasing the LMN threshold to <2.5, would result in a sensitivity of 93.3% in our cohort. Further validation in a prospective cohort of influenza patients would be helpful in identifying the optimal cut-off for the LMR to support a diagnosis of influenza respiratory tract infection. In this age of antimicrobial resistance, validation of such indices may also have antibiotic stewardship implication, apart from early identification of high-risk individuals who may benefit from early neuraminidase inhibitors.

**Table 1**
Laboratory characteristics of PCR-proven cases of influenza infections.

| Patient No | White Blood Cell Count (4.00 – 10.00 x $10^9$/L) | NLR | LMR | Platelet Count (140 – 440 x $10^9$/L) | Procalcitonin (≤0.49 ug/L) | C-reactive protein (0.2 – 9.1 mg/L) |
|---|---|---|---|---|---|---|
| 1 | 7.00 | 4.1 | 1.1 | 266 | 0.09 | 11.8 |
| 2 | 7.12 | 6.9 | 0.68 | 223 | 0.11 | Nil |
| 3 | 5.53 | 3.5 | 1.3 | 148 | Nil | Nil |
| 4 | 4.79 | 8.8 | 2.2 | 199 | 0.07 | Nil |
| 5 | 7.16 | 4.4 | 1.2 | 186 | Nil | Nil |
| 6 | 6.67 | 2.9 | 2.4 | 179 | 0.56 | 13 |
| 7 | 7.87 | 10.3 | 1.6 | 192 | 0.24 | 202 |
| 8 | 5.10 | 3.1 | 1.5 | 138 | <0.06 | 3.2 |
| 9 | 6.89 | 5.3 | 1.5 | 137 | 20.8 | Nil |
| 10 | 7.65 | 12.6 | 0.52 | 133 | 0.16 | Nil |
| 11 | 5.35 | 12.9 | 0.85 | 197 | <0.06 | 9.5 |
| 12 | 4.46 | 2.7 | 1.9 | 96 | 0.07 | 10.2 |
| 13 | 8.33 | 4.9 | 1.2 | 229 | 0.08 | 157 |
| 14 | 10.00 | 6.8 | 5.6 | 142 | 1.00 | Nil |
| 15 | 4.11 | 5.7 | 0.73 | 101 | Nil | 0.3 |

## Conflict of interest

None.

## Acknowledgements

None.

## References

1. Rusell C.D., Parajuli A., Gale H.J., Bulteel N.S., Schuetz P., de Jager C.P.C., et al. The utility of peripheral blood leucocyte ratios as biomarkers in infectious diseases: a systematic review and meta-analysis. *J Infect* 2019;**78**(5):339–48.
2. Troeger C., Blacker B.F., Khalil I.A., Rao P.C., Cao J., Zimsen S.R.M., et al. GBD 2016 respiratory infections collaborators. Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the global burden of disease study 2016. *Lancet Infect Dis* 2018;**18**(11):1191–210.
3. Low D.. Reducing antibiotic use in influenza: challenges and rewards. *Clin Microbiol Infect* 2008;**14**(4):298–306.

S Zheng
*Department of General Medicine, Sengkang General Hospital. 110 Sengkang E Way, Singapore, 544886. Singapore*
*E-mail address:* zheng.shuwei@singhealth.com.sg

Accepted 8 June 2019
Available online 12 June 2019

https://doi.org/10.1016/j.jinf.2019.06.003

© 2019 The British Infection Association. Published by Elsevier Ltd. All rights reserved.