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*Original Research Article*

## Point of care lung ultrasound for early diagnosis and progress (prognostication) of H1N1 infections: a case series of 11 patients

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Severe infection with the H1N1 virus (commonly known as swine flu) often results in acute severe respiratory distress that require early and aggressive treatment to reduce the case fatality, transmission rate and overall morbidity and financial burden. Traditional definitive diagnostic test from sputum, nasal and pharyngeal swab takes a minimum of 24-48 hours to get the result. We observed some characteristics ultrasonic signs such as loss of visceral and parietal pleural interface, subpleural bleb, bunch of grapes sign on lung ultrasonography on a consistent basis in patients with acute viral pneumonia of H1N1 infection. Being a non-invasive, bedside tool, USG gives real time finding and diagnosis on spot unlike other radiologic and laboratory test, where it takes some turn out time to get the report. As rapid diagnosis and antiviral treatment or is one of the main determinants of outcome of Acute H1N1. Point of care Lung US in the emergency department and ICU can help in rapid diagnosis and monitoring of disease progression and treatment responsiveness of acute infection with H1N1.

**Key words:** Point of care, H1N1 infection, Lung ultrasound, Visceral Parietal Pleural Interface, Subpleural Bleb, Bunch of grapes.

### INTRODUCTION

In late March and early April 2009, an outbreak of H1N1 influenza a virus infection was reported from Mexico, which subsequent spread out of America continent like an epidemic to a pandemic form in many other countries, including Asia, Australia. In June 2009, the World Health Organization (WHO) raised its pandemic alert level to the highest level, phase 6, indicating widespread community transmission on at least two continents (1-3). The pandemic was declared to be over in August 2010 but it is still endemic in the South-East Asia.

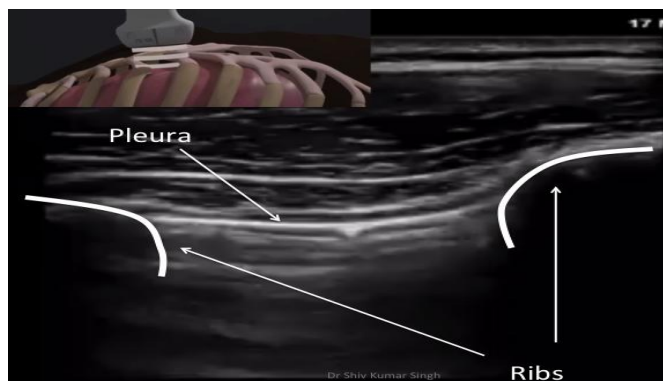
Early diagnosis and prompt treatment not only reduces mortality and morbidity but also save huge amounts of funds in term of financial burden. The definitive diagnosis of H1N1 infection is based on lab results that can take minimum of 24-48hrs or even longer (4). Ultrasonography of the lung is gaining popularity to diagnose a variety of pulmonary pathology including pneumonia (5-8). Lots of publications in literatures favor the use of Lung ultrasonography to diagnose diverse causes of acute pulmonary pathology like effusion,

pneumothorax, pneumonia, pulmonary edema, obstructive airway disease etc as a rapid, non-invasive, repetitive and bedside technique (9-13). Lung ultrasonography is commonly done in our set up for any patient presenting with acute respiratory distress who needs intensive care unit (ICU) admission. We observed some characteristic ultrasonic signs on lung ultrasonography on a consistent basis in patients with acute viral pneumonia of H1N1 infection. Early clinical suspicion and timely initiation of antiviral therapy might be the main determinant factor for low mortality in H1N1 infection.

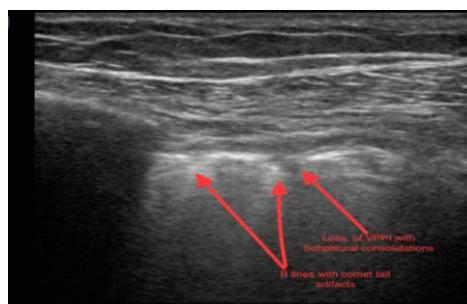
Being a non-invasive, bedside tool, USG gives real time finding and diagnosis on spot unlike other radiologic and laboratory test, where it takes some turn out time to get the report. This is our effort to highlight the importance of sonographic finding for early detection and initiation of antiviral treatment in which is one of the critical determinant of mortality in severe viral infection like H1N1.

Case no	Age	Sex	Time to lung US	Time to start of Temiflue
1	22	F	Within 1 HR In ED	6HR
2	35	M	Within 1 HR In ED	6HR
3	44	M	Within 1 HR In ED	6HR
4	28	M	In ICU (4 Hr)	10HR
5	38	M	In ICU (10 Hr)	10HR
6	55	M	within In ED	6HR
7	64	M	Within 1 HR In ED	<6HR
8	44	F	Within 1 HR In ED	<6HR
9	31	F	Within 1 HR In ED	<6HR
10	29	F	Within 1 HR In ED	<6HR
11	36	M	In ICU (12hr)	24HR

**Table 1:** Demographic profile and first lung US scanning and time to first Antiviral treatment received



**Image 1:** Normal Visceral Parietal Pleural Interface (VPPI)



**Image 2:** Discontinuity of pleural line with subpleural minute consolidations

### Cases under study

We tried to analyze and correlate some of the sonographic findings in a retrospective way with the severity of infection and the laboratory confirmation of H1N1 infection. US finding was not used as definitive diagnostic criteria for the H1N1 infection.

From March 2014 to March 2015, (over one year) we collected data from 11 patients of suspected H1N1 infection. A consultant trained in use of lung sonography did the US study in all the 11 cases. Finding were recorded based on the Visceral Parietal Pleural Interface (VPPI) appearance in the 3th - 4th rib interspace in midclavicular line and in the 6th - 7th rib

in mid axillary line. All the 11 proven cases exhibited same characteristic lung sonographic finding on a consistent basis. Based on strong clinical and sonographic finding all the 11 cases were put on empirical antiviral therapy (temiflu) and the majority of the patients (8/11) recovered from the deadly H1N1 infection without any sequel. Our consultant in-charge for ICU is well trained in lung US. All the 11 patients included in our analysis, the lung US was done either in Emergency before shifting to ICU or after shifting to ICU depending on the time of patient arrival and availability of the concern ICU consultant for the sonography. Out of 11 patients, 8 patients were evaluated with sonography within 1 hour of hospital arrival, it took 4 hours for 1 patient and 2 patients were evaluated at 10-12 hour after hospital admission. 7 patients were male and 4 patients female with age ranging from 22-66. (Table 1)

The lung US findings were recorded and based on this finding, a strong clinical suspicion of H1N1 infection was made and immediately, throat and nasal swab sample were taken for laboratory confirmation by Polymerase Chain Reaction (PCR). The results of the swabs were only available after 48 hours as per our local facility. Based on the lung findings, all cases were started on Antiviral treatment with Oseltamavir (Tamiflu). Treatment was commenced in most cases in less than 12 hours of admission to the hospital except for the 11th case where the treatment was commenced within 24hrs (Table-2).

### Ultrasonographic findings

In a normal lung, we look at the typical Visceral Parietal Pleural Interface (VPPI) by placing the probe in the 3rd/ 4th Intercostal space mid-clavicular line and 6th/7th Intercostal space mid-axillary line where we can see the pleural sliding sign, common taught to all for recognizing pneumothorax where it is absent. (Image 1)

The characteristic VPPI findings in H1N1 are not only unique but are easily detectable by high frequency linear probe. The probe is placed exactly like it is done in normal Lung Ultrasound imaging. The changes that are seen in H1N1 infection are seen in the subpleural space and we describe these as subpleural consolidations "Subpleural bunch of grapes". These characteristic findings are due to fluid (pus) filled blebs that create disruptions in the pleural lines (Seen as continuous parallel lines sliding over each other in normal lungs). It can be described as B profile lung with multiple B lines (Comet tail artifacts) going in different directions. There is always a discontinuity of VPPI (pleural line) because of pathological processes. (Image: 2)

All the 11 cases described in this case series had the typical "Subpleural bunch of grape" sign on lung ultrasound; this is due to multiple subpleural collection and consolidation due to acute H1N1 infection. (Image: 3)

All the 11 patients who had the characteristic lung findings and based on these findings all the 11 cases were started on antiviral medication (Temiflu 150mg BID). Surprisingly, all had positive PCR results for H1N1 infection on nasopharyngeal swabs.

Clinical severity and progress: Daily Ultrasonographic evaluations were done in ICU by the same consultant doing the primary scanning. Patient showing clinical improvement also exhibited progressive resolution of the lung sign with normal VPPI pattern. Whereas, patient worsening clinically

because of overwhelming infection or secondary bacterial infection, the lung changes progress to hepatisation, no pleural lines is seen. (Image 4)

All the 11 cases needed positive ventilator support; non-invasive ventilation (NIV) was initially attempted in few patients presenting with mild to moderate respiratory distress, but most cases ended up with tracheal intubation and invasive ventilation because of worsening in respiratory parameters except one case (case no 8), who was solely managed with the NIV. (Table 3) Of the 11 cases with poor outcomes, most (4/5) were intubated in the ED itself suggesting rapid progress or late presentation.

The average ICU stay was 9.7 days. Of the 11 patients, those who did not survive (3/11), all had risk factors that are associated with high morbidity and mortality. The 1st patient was a pregnant female patient. One male patient had chronic renal failure (CRF) and was a chronic smoker. The third patient was morbidly obese males, chronic alcoholic and smoker. Amongst the patients who made a good recovery (8/11), four had no risk factors and rest four were obese, but without any other comorbidity, suggesting that obesity on its own is not a significant risk factor but in combination with chronic smoking increases the morbidity and mortality related to H1N1 infection. (Table 4)

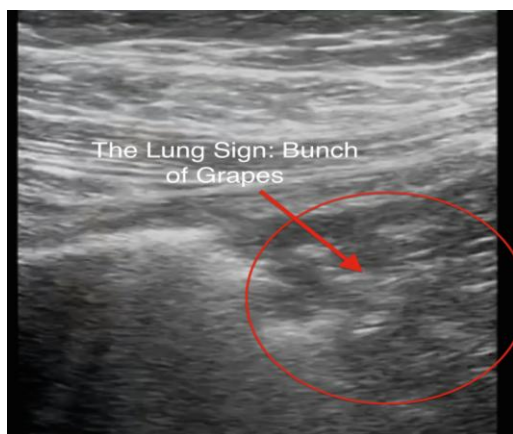
In patients with poor outcomes, there is a clear trend that either patient has rapid deterioration leading to death within 24 – 48 hrs or if they survive the first few days, they have prolonged stay and die of multi-organ failure.

### Discussion

The average time for laboratory to provide PCR results is 48 hours (Nasopharyngeal swabs) but ultrasound prediction is instant on arrival (It takes less than 5 min for one lung ultrasound examination) (14, 15). With this small case series showing 100% accuracy in predicting H1N1 infection using lung ultrasound, will not only help in commencing early treatment that will result in early patient care but also help healthcare personal taking precautions.

The only test that is available to us and many others in the South East Asia for diagnosis of H1N1 infection is Polymerase Chain Reaction (PCR). Nucleic acid amplification tests, such as rRT-PCR, are the most sensitive and specific tests for the diagnosis of influenza virus infection. However, they are often not readily available and/or may require several days for processing since many hospitals must send samples to be processed in public health or commercial laboratories (16, 17). Test performance depends on the individual rRT-PCR assay used, as well as the quality of the sample obtained.

One study, which compared the use of combined nasopharyngeal and throat swabs (CNTS) with nasopharyngeal aspirates (NPA) using rRT-PCR, showed that CNTS had the highest sensitivity and that the use of both CNTS and NPA had a higher sensitivity than either method alone (18). In another a multicenter study from China, the median length of time during which patients had a positive rRT-PCR was six days (range 1 to 17 days). Independent risk factors for prolonged rRT-PCR positivity included age <14 years, male gender, and a delay from onset of symptoms to treatment with oseltamivir of >48 hours (19).



**Image 3:** Bunch of Grapes appearance in lung US.



**Image 4:** US scanning of lung showing hepatisation in superimposed bacterial infection

CASE	AGE	SEX	RESPIRATORY SUPPORT
1	22	F	NIV on day 1, Intubated DAY 2
2	35	M	NIV on day 1–Intubated Day 2
3	44	M	Intubated in ED on day 1
4	28	M	Intubated in ED on day 1
5	38	M	NIV on day 1 –Intubated Day 2
6	55	M	NIV on day 1–Intubated Day 2
7	64	M	Intubated in the ED-day 1
8	44	F	NIV- day 1
9	31	F	NIV initially–Intubated Day 1
10	29	F	NIV day 1 –Intubated Day 2
11	36	M	Intubated In ED- day 1

**Table 3:** Respiratory Support; Location, timing and type of ventilator support

Among 35 patients in the United States with confirmed pandemic H1N1 influenza A infection, the median duration of virus detection from nasopharyngeal specimens by rRT-PCR was 4.2 days, which was similar to the duration of fever (3.5 days) but shorter than the duration of cough (11 days); however, few specimens were collected between days five to nine (20).

Typical clinical manifestations of pandemic H1N1 influenza and infection included fever, headache, cough, sore throat, myalgias, chills, and fatigue; vomiting and diarrhoea were also common, both of which are unusual features of seasonal influenza. Since these manifestations are similar to any viral infections, it is not uncommon for patients to present late to the hospitals (19-21). On top of this, getting lab results

for H1N1 can take nearly 48 hrs. Having a sensitive non-invasive method for diagnosing H1N1 infections not only helps in initiating treatment, but also reduces the cost of hospital stay in patients who have no co-morbidities (low risk factors).

The Sonographic feature of loss of VPPI, bunch of grapes appearance might be due to extensive central plus peripheral lung involvement in acute viral infection. The bacterial infection tends to be central and more localised distribution in the initial phase. Considering the rapidity of appearance of clinical symptoms in the background of H1N1 endemic zone, first differential diagnosis certainly comes as H1N1 infection. However, any rapidly progressing viral infection may present the similar clinical and US imaging.

With this small case series showing 100% accuracy in predicting H1N1 infection using lung ultrasound, will not only

help commencing early treatment that will result in early patient care but also help healthcare personal taking precautions.

CASE	AGE	SEX	RISK FACTORS	OUTCOME	LOS (DAYS)
1	22	F	Pregnant	Died	18
2	35	M	Obese	Discharged	5
3	44	M	Obese + Smoker+ alcoholic	Died	22
4	28	M	Obese	Discharged	16
5	38	M	Nil	Discharged	6
6	55	M	Nil	Discharged	10
7	64	M	Renal failure + Smoker	Died	2
8	44	F	Obese	Discharged	4
9	31	F	Nil	Discharged	5
10	29	F	Nil	Discharged	9
11	36	M	Obese	Discharged	10

**Table 4:** Risk factors, Outcomes and Length of Stay

In a study of 100 fatal cases of pandemic H1N1 influenza A, severe tracheobronchial injury with diffuse alveolar damage and haemorrhage were present in almost all cases. Underlying medical conditions and bacterial co-infections contributed to the fatal outcome of this infection (22). Using lung US scanning, helps in detection and monitoring of early sign of severe viral pneumonia as well to detect the early sign of secondary bacterial infection. Ultrasonography has been used in detection of H1N1 infection (23, 24).

### Challenges With H1N1 Infection

There are still challenges that we face with treating H1N1 infections. Large studies have shown that the speed of diagnosing and antiviral treatment initiation following symptom onset are significantly associated with disease severity and death. Optimal survival and minimal disease severity appear to result when antivirals are started as soon as possible after symptom onset (25, 26). Inability to diagnose early and failure to initiate treatment may be a crucial determinant of the severity and outcome of H1N1.

### Limitation in the study

This study involved only few number of patient which is a major limitation in this study.

### Conclusion

As rapid diagnosis and antiviral treatment is one of the main determinants of outcome of Acute H1N1. Point of care Lung US in the emergency department and ICU can help in rapid diagnosis and monitoring of disease progression and treatment responsiveness of acute infection with H1N1. A high degree of suspicion is critical, especially in the absence of rapid testing method, and should prompt empiric antiviral therapy. With widespread use in bedside sonography, more definitive and specific sonographic findings may emerge in near future that will help in diagnosing acute viral infection on spot.

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