August-2024

Clinical Trial Protocol

Administrative information

Title

1- Effect of Pediatric Lung Ultrasound on Antibiotic Prescriptions in Hospitalized Children and Adolescents with Lower Respiratory Tract Infections. A Randomized Controlled Trial.
"PLUS-AP Trial"

Trial registration

2a- Intended registry: ClinicalTrials.gov

2b- WHO Trial Registration data

Data category	**Information**
Primary registry and trial identifying number	ClinicalTrials.gov
Date of registration in primary registry	TBD
Secondary identifying numbers	-
Source(s) of monetary or material support	American University of Beirut Medical Center (AUBMC)
Primary sponsor	American University of Beirut (AUB) – University Research Board (URB) AUBMC - Medical Practice Plan (MPP)
Secondary sponsor(s)	none
Contact for public queries	Ali Ismail: ai18@aub.edu.lb
Contact for scientific queries	Ali Ismail: ai18@aub.edu.lb
Public title	Lung ultrasound (LUS) effect on antibiotic prescriptions in children with lower respiratory tract infections (LRTIs).
Scientific title	Effect of Pediatric Lung Ultrasound on Antibiotic Prescriptions in Hospitalized Children with Lower Respiratory Tract Infections. A Randomized Controlled Trial. "PLUS-AP Trial"
Countries of recruitment	Lebanon
Health condition(s) or problem(s) studied	-Antibiotic prescriptions to children and adolescents with viral LRTIs

	-Differentiation between viral and bacterial LRTIs with the help of LUS
Intervention(s)	(Lung ultrasound "LUS" + standard treatment) vs. (Sham lung ultrasound "SLUS" + standard treatment)
Key inclusion and exclusion criteria	Age eligibility for study: 3 months -18 years Gender eligibility for study: both males and females Accepts healthy volunteers: no Inclusion criteria: - Age between 3 months and 17 years old inclusive -Currently admitted to the pediatric Ward or boarding in the Emergency Department within 24 hours of admission order due to lower respiratory tract infections. Exclusion criteria: -Sickle cell disease (SCD). -On chemotherapy or any other immunosuppressive therapy except systemic corticosteroids use of ≤ 5 days duration. -Cystic fibrosis and other chronic lung diseases except asthma -Pre-existing and/or congenital neurologic, metabolic, and cardiac conditions -Hospitalized within the previous month - Patients with suspected foreign body aspiration -Received antibiotic therapy within the previous week -Patients admitted under PI's care
Study type	Interventional Allocation: randomized Intervention model: parallel assignment Blinding: -Patients will be blinded to LUS vs SLUS. -Principal Investigator (PI), who will solely be doing LUS, will be blinded to CXR findings. Data analyst, Dr. Ziad Mahfoud will be blinded to patients' allocation. Primary purpose: prevention Phase III
Date of first enrolment	TBD
Target sample size	176 patients (88 in each arm)
Recruitment status	Not yet

Primary outcome	-Antibiotic prescriptions rate upon discharge in hospitalized children and adolescents with LRTIs on standard care who undergo LUS vs. SLUS
Secondary outcomes	-Length of stay (LOS) in the hospital -Rate of complications by 4 weeks after enrollment: admission to ICU, chest tube insertion, mortality -Frequency of chest x-ray (CXR) performance by 4 weeks after enrollment. -The rate of antibiotic intake, evaluated 4 weeks following enrollment.

Table 1: WHO Trial Registration data

Protocol version

3- Date and version identifier: first version dated August 26, 2024.
Issue Date: August 26, 2024
Protocol Amendment Number: N/A
Revision Chronology: N/A

Funding

4- This protocol has received financial support from the University Research Board (URB) and Medical Practice Plan (MPP) at the American University of Beirut (AUB). The grant specifically covers the salary of a research fellow and hospital equipment charges. The funding body has no role in the design of the study, collection, analysis, interpretation of data, or in writing the manuscript.

Roles and responsibilities

5- a- Names, affiliations, and roles of protocol contributors:
Ali Ismail (A.I.), M.D. (PI); Marianne Majdalani (M.M.), M.D. (Study Coordinator); Hawraa Roof (H.R.), M.D. (Co-I); Dima Khreis (D.K.), M.D. (Co_I); Maysaa Slika (M.S.), M.D. (Co_I) M.D. (Co-I); Jihane Moukhaiber (J.M.), M.D. (Co-I); Jana Ayyash (J.A.), Medical student at AUB (Co-I); Ziad Mahfoud (Z.M.), Biostatistics (Collaborator), Rita Sebaaly (R.S.), Medical student at AUB (Co-I); Sana Kalaji (S.K.), Medical student at AUB (Co-I); Mohamad Hassan (M.H.), Medical student at AUB (Co-I).
A.I. leads protocol development, oversees study implementation, data entry, analyses, manuscript writing and publication. A.I. will be responsible for data integrity.
Ali Hijazi, a medical student at Balamand University and independent from the study team, will be responsible for the randomization sequence and giving the allocation by phone.

All Authors will contribute to study conduct, and manuscript writing. ZM will do the statistical analysis.

b- Name and contact information for the trial sponsor:
Trial Sponsor: AUB funds - URB
Sponsor's Reference: award/project 104524
Contact name: Mazen Al-Shami
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c- The funding source did not play a role in the study's design and will not be involved in its execution, data analysis, interpretation, or decision to submit results.

d- Committees:
Trial Steering Committee (TSC): The Trial Steering Committee will consist of the following investigators: **Ali Ismail** (A.I.) – Principal Investigator (PI), **Marianne Majdalani** (M.M.), **Jihan Mkhaiber** (J.M.), **Maysaa Slika** (M.S.), **Hawraa Raouf** (H.R.), **Dima Khreis** (D.K.), Co-Principal Investigators. And **Ziad Mahfoud** (Z.M.) – collaborator and Co-Principal Investigator.
The responsibilities of the trial steering committee include the following:

1. Recruitment of patients and coordination with the principal investigator.
2. Regularly reviewing the progress of the study (weekly).
3. If necessary, agreeing upon changes to the protocol and/or investigators brochure to ensure the study runs smoothly.

Data and Safety Monitoring Committee (DSMC).
The chair of the DSMC is going to be Dr. Mona Nabulsi (Pediatrician, Department of Pediatrics and Adolescent Medicine, AUBMC) with two members: Dr. Lama Charafeddine (Neonatologist, Department of Pediatrics and Adolescent Medicine, AUBMC), and Dr. Hani Tamim (Biostatistician, Clinical Research Institute, AUB).

Introduction

Background and rationale

6a- Lower Respiratory Tract Infections (LRTIs) are a substantial global health concern associated with a high morbidity and mortality.[1] According to Unicef, in 2022 more than 2000 children under 5 years of age died every month because of pneumonia globally and mostly in the developing countries, where pneumonia is the number one cause of death. Immunization against

streptococcus pneumonia and Haemophilus Influenza-type b lead to a significant drop in the related mortality.[2,3]

Children under the age of 5 years have the highest rate of hospitalization due to pneumonia. When multiple pathogens were tested for diagnostic purposes, it was found that 81% of the children with pneumonia had at least one pathogen detected. Among these children, viral pathogens were identified in 66% of cases, bacterial pathogens were detected in 8% of cases, while both viral and bacterial pathogens in 7%.[4]

Many, if not most, children with viral LRTIs are receiving incorrect treatment with antibiotics.

A retrospective study conducted in Canada examined 131 hospitalized children aged 1-24 months with bronchiolitis. The findings revealed that approximately 44% of the patients were given antibiotics as part of their management.[5]
In 2022, a retrospective multicenter study conducted in Pakistan examined 5,926 hospitalized children with lower respiratory tract infections. The study revealed that all of the children, representing 100% of the cases, were prescribed antibiotics as part of their treatment.[6]

The latest guidelines from CDC on the management of community acquired pneumonia recommended against using antibiotics in children with viral pneumonia in the absence of findings suggestive of bacterial coinfection.[7] British Thoracic Society, on the other hand, in 2011 recommended to treat all children who have pneumonia with antibiotics because they found it difficult to reliably differentiate between viral and bacterial pneumonia. They emphasized on the need to detect the etiologic organism in those patients and to seek for better diagnostic methods.[8]

Antibiotic stewardship programs place emphasis on avoiding the unnecessary use of antibiotics to reduce the risk of antibiotic resistance, which poses a threat to public health.[9]

Comparative studies conducted in pediatric populations show that point of care LUS has a better diagnostic accuracy than, physical examination and CXR in diagnosing various respiratory tract diseases. These include pneumonia, bronchiolitis, pneumothorax, pulmonary edema, acute chest syndrome, pleural effusion, and pulmonary contusion.[10]

In recent years, efforts have been made to assess the utility, reliability and efficiency of LUS in the proper diagnosis of community acquired pneumonia (CAP) in children.[11] A meta-analysis in 2015 of 8 studies, published by the American Academy of Pediatrics (AAP), showed that LUS had a sensitivity of 96% and a specificity of 93% in the diagnosis of pneumonia in children when compared to CXR as a reference standard. Indeed, they proposed to use LUS as an alternative method to CXR for the evaluation of pneumonia in children.[12] Another meta-analysis came out in 2019 by Heuvelings et al. and included 30 well conducted studies, went further in the evaluation of children with suspected pneumonia and suggested that LUS should replace CXR as a first-line imaging study.[13]

Differentiating between viral and bacterial etiology in children with CAP is crucial for initial management, and lung ultrasound proves highly beneficial in this regard.[10,14–17] In a prospective study that was published in Nature Scientific Reports in 2019 and included 147 hospitalized children with CAP, Berce et al. stratified patients according to the microbiological results and described the differences in LUS findings between bacterial and viral pneumonia. In bacterial CAP, the consolidations were more likely to be solitary, larger, and unilateral compared to those observed in viral CAPs.[14] The combination of epidemiological, clinical, and laboratory data greatly enhances the usefulness of lung ultrasound. In 2022 Omran et al. described the effectiveness of LUS with and without the neutrophil-to-lymphocyte ratio (NLR) in early detection and differentiation of viral and bacterial pneumonia in young children from Egypt. In this prospective study LUS exhibited superior sensitivity and specificity in detecting bacterial pneumonia compared to CXR. LUS demonstrated sensitivities of 88.2% for bacterial pneumonia and 83.3% for viral pneumonia, while CXR showed sensitivities of 70.6% for bacterial pneumonia and a lower sensitivity of 33.3% for viral pneumonia. In terms of specificity, LUS had a specificity of 85.7% for viral pneumonia and 100% for bacterial pneumonia, whereas CXR had specificities of 78.5% for viral pneumonia and 85.7% for bacterial pneumonia.[15] A cluster randomized clinical trial that was conducted in adults with LRTIs, showed that doing LUS in addition to procalcitonin level, when compared to standard care, resulted in a significant 26% decrease in the likelihood of receiving a 28-day antibiotic prescriptions, while maintaining patient safety.[18]

The prevalence of bacterial pneumonia among hospitalized patients with lower respiratory tract infections (LRTIs) is higher in adults compared to children, with rates of 66% in adults[18] and 15% in children.[4]

Studies in children examining the use of procalcitonin to differentiate between bacterial and viral etiologies have yielded inconsistent findings due to the diverse methods employed and variations in the reference standards used to determine the cause such as blood culture versus polymerase chain reaction testing (PCR).[19]

The integration of anatomical and/or physiological information obtained through point of care ultrasound with clinical and laboratory data enables the making of timely and accurate decisions.[20]

There isn't enough evidence in the literature on the benefit of adding LUS to standard care in decreasing the prescription rate of antibiotics upon discharge in hospitalized children with LRTIs.

We hypothesize that among hospitalized children due to lower respiratory disease, doing a lung ultrasound in addition to standard care as compared to simulated Sham LUS (SLUS) with standard care is associated with less prescriptions of antibiotics upon discharge while maintaining patient safety. Complications of LRTIs (ICU admission, chest tube insertion, mortality, readmission to the hospital) can occur in those patients who will not receive a timely etiology treatment, in particular antibiotics in the case of bacterial pneumonia. We will repeat LUS 48 hours after enrollment or upon discharge whichever comes first, to ensure patients' safety. Evaluation of the

primary endpoint will be done by assessing the rate of antibiotic prescriptions upon discharge. As for the secondary endpoints, we will evaluate patient safety by examining the length of hospital stay, complications of LRTIs (ICU admission, chest tube insertion, mortality), and the rate of readmission to the hospital and antibiotic intake along with the rate of chest X-rays performed within 4 weeks of enrollment.

LUS offers several benefits, including the absence of ionizing radiation, reduced expenses, the potential for subsequent examinations, the ability to track treatment progress, and improved patient collaboration. Additionally, this diagnostic method is readily available, portable, rapid, user-friendly, and can be promptly employed as a point-of-care approach.[20]

6b- Despite the high evidence on the role of LUS in the management of children with LRTIs, it is still not part of the standard care in Lebanon. The standard care includes taking the patient's history, physical exam, CXR and laboratory workup. Sham ultrasound can be done safely in the control group, where patients will get the standard care. The safety of LUS is well established and do not expose patients to any harm or risk.[20]

Objectives

7- Specific objectives or hypotheses

- Research Hypothesis: The addition of LUS to standard care in hospitalized children with LRTIs, will result in a notable reduction in the rate of antibiotic prescriptions, compared to SLUS and standard of care while maintaining patient safety.
- Study objectives:
    - Primary objective: To investigate the effect of adding LUS to standard care on the endpoint of antibiotic prescriptions upon discharge in children hospitalized with LRTIs, compared to standard care and SLUS.
    - Secondary objectives: To investigate the effect of adding LUS to standard care, as compared to standard care with SLUS, on the end points of:
        - Length of stay in the hospital
        - Rate of complications by 4 weeks after enrollment: admission to ICU, chest tube insertion, mortality
        - Frequency of CXR performance within 4 weeks of enrollment
        - Rate of antibiotic intake assessed 4 weeks after enrollment
        - Rate of hospital readmission within 4 weeks of enrollment.

Trial design

8- The PLUS-AP trial is designed as a phase III, randomized, controlled, blinded, single center superiority trial with two parallel groups and a primary endpoint of antibiotic prescriptions by the day of discharge from the hospital. Randomization will be performed as permuted block randomization with a 1:1 allocation.

Methods: Participants, interventions, and outcomes

Study setting

9- Selection of Countries: The study will take place in the capital city of Lebanon Beirut. It is mainly an urban area with few rural areas around it. The population is estimated to be around 2.4 million people. It represents a diverse population that includes a significant number of refugees and displaced people from Syria and Palestine. This adds complexity to the economic, social and healthcare systems. The American University of Beirut Medical Center (AUBMC), a tertiary prestigious academic institution in the region that provides high-quality medical care, education and research, is the only site of our trial.

Eligibility criteria

10- Inclusion criteria: Patients eligible for the trial must provide a written informed consent before any study procedures and comply with all of the following at randomization:
    - Age between 3 months and 18 years
    - Currently admitted to the Pediatric Ward or boarding in the Emergency Department within 24 hours of admission order due to LRTIs.
- Exclusion criteria:
    - Sickle cell disease (SCD).
    - On chemotherapy or any other immunosuppressive therapy, except systemic corticosteroids use of ≤ 5 days duration.
    - Cystic fibrosis and other chronic lung diseases except asthma.
    - Pre-existing and/or congenital neurologic, metabolic, and cardiac conditions
    - Hospitalized within the previous month
    - Patients with suspected foreign body aspiration
    - Received antibiotic therapy within the previous week
    - Patients admitted under the PI's care

Interventions

11a- Eligible patients will be randomized between LUS and sham LUS (SLUS) groups. The bedside LUS will be exclusively performed by the principal investigator (A.I.), who has credentialing in LUS with more than 5 years of experience, and will be blinded to CXR results. The LUS or SLUS

will be done at his earliest convenient time, within a maximum of 24 hours of enrollment and will be repeated 48 hours after the first ultrasound or before discharge from the hospital whichever comes first. The PI will explain to the family the procedure of the LUS before conducting it without telling them the results nor whether it is LUS or SLUS. Since the patients are seen after being admitted to the hospital, these patients undergo standard care including history taking, physical exam, laboratory workup and CXR in the emergency Department (ED) as deemed necessary by the primary physician.

In the LUS group: AI will make sure to have adequate depth of the ultrasound image (at least double the distance from skin to the pleural line in order to be able to assess reverberation artifacts – A-lines). He will scan each lung in the longitudinal and transverse orientation views in the midclavicular line anteriorly, paraspinal line posteriorly, and the mid-axillary line for a total of six scanning zones as described by Copetti and Cattarossi.[21] The ultrasound findings will be assessed and recorded on a data collection form (Appendix III) and will be interpreted immediately after finishing LUS and will be communicated to the patient's attending physician who will decide on what changes in the management of patients will take place.

To perform a proper lung ultrasound, the image depth should be at least twice the distance from the skin to the pleural line. A depth of 1 cm is never adequate for this purpose. In the SLUS group, we will deliberately use a shallow image (1 cm depth) to mimic LUS without the capability to detect lung pathology, while ensuring that the same areas of the chest wall are covered in the same amount of time as a complete LUS.

11b- No Criteria for discontinuing or modifying allocated interventions for a given trial participant.

11c- Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence are not applicable to our trial because it is a one-time occurrence.

11d- Relevant concomitant care and interventions that are permitted or prohibited during the trial

- All kinds of standard care for children with LRTIs will be allowed in the controlled group except doing lung ultrasound.

Outcomes

12-

- Primary outcome:
  - Antibiotic prescriptions rate upon discharge in hospitalized children and adolescents with LRTIs who undergo LUS vs. SLUS, both in addition to standard care. Patients who will receive antibiotics for ≤ 48 hours before enrolment and will stop it after enrolment will be considered not taking antibiotics since this short course will not affect the outcome of a bacterial LRTI.

- Secondary outcome:
  - Length of stay in the hospital
  - Rate of complications (by 4 weeks after enrollment will be analyzed as single outcomes): admission to ICU, chest tube insertion, mortality
  - Frequency of chest x-ray (CXR) performance by the 4 weeks after enrollment.
  - The rate of antibiotic intake, evaluated 4 weeks after enrollment.
  - Rate of readmission to hospital by 4 weeks after enrollment

Participant timeline

13-

Study Period								**Close-out**
	Enrollment	Allocation	Post-Enrollment					
Time Point	0	1st 24 hours	1st 24 hours	3rd day or upon discharge whichever comes 1st	1 week	2 weeks	3 weeks	4 weeks
Eligibility screen	x							
Informed consent	x							
Allocation		x						
LUS			x	x				
SLUS			x	x				
Phone call					x	x	x	x

Table 2: Participant timeline

Sample Size:

14- The sample size was determined based on the primary hypothesis.

At our institution, the rate of antibiotic prescriptions for hospitalized children with LRTIs is approximately 60%. In the PLUS-AP trial, we anticipate that performing Lung Ultrasound (LUS)

will lead to a 25% reduction in the rate of antibiotic prescriptions in the LUS arm. Specifically, this means that while 60% of children in the SLUS arm are expected to receive antibiotics, we expect that only 35% of children in the LUS arm will be prescribed antibiotics. This reduction is expected without the addition of procalcitonin testing.

The primary study endpoint will be assessed upon discharging the patient from the hospital, that's why a very minimal percentage (5%) is anticipated to have loss to follow-up. To ensure adequate statistical power (80%) and a significance level of 5%, we used SPSS to calculate the sample size using proportions and the independent samples binomial test. The calculated sample size for each arm is 62 patients. Accounting for a potential 5% loss to follow-up, the adjusted sample size is 66 patients in each arm. Therefore, a total of 132 patients will be required to recruit for the study. The variability in antibiotic prescriptions among the 11 pediatricians in our institution can be attributed to their differing practices rather than patient-related factors. When determining the sample size, we have assumed that the clustering occurs by physician, resulting in 11 distinct clusters. As there are no similar studies available, the specific intra-class correlation coefficient (ICC) is currently unknown. However, limited comparable studies have indicated that the ICC typically falls within the range of 0.01 to 0.07.[22,23] For our trial, we have conservatively estimated the ICC to be 0.03. By using the formula 1 + (M-1) ICC, where M represents the average cluster size (which is 12 patients per physician, calculated as 132 patients divided by 11 physicians), the design effect (DE) was computed to be 1.33. Consequently, the average cluster sample size is calculated as 132 multiplied by the DE (1.33), resulting in 176 patients (or 88 per arm). Table 3 shows different scenarios of sample size based on different effect size and different power.

Effect Size	Alpha	Power	Loss to follow-up	Sample Size (Arm)	Total Sample Size	P	k	Design Effect	Sample Size (Arm)	Adjusted Sample Size
25%	0.05	80%	5%	66	132	0.03	11	1.33	88	176
25%	0.05	90%	5%	87	174	0.03	11	1.33	116	232
20%	0.05	80%	5%	101	202	0.03	11	1.33	134	268
20%	0.05	90%	5%	135	270	0.03	11	1.33	180	360
15%	0.05	80%	5%	179	358	0.03	11	1.33	238	476
15%	0.05	90%	5%	239	478	0.03	11	1.33	318	636

Table 3: Sample size based on different scenarios of effect size estimates and power

Recruitment

15- To identify eligible patients for the PLUS-AP Trial, the Principal Investigator (PI) will circulate the IRB-approved protocol to all attending physicians who admit patients to the pediatric ward. During a divisional meeting, the PI will present the protocol to familiarize colleagues with its

implementation, gather valuable feedback to enhance the study's execution, and seek their agreement to allow the research team to approach eligible patients under their care whenever they are admitted.

During the trial, co-investigators, excluding the PI (who will remain blinded to chest X-ray findings), will conduct daily screenings by inquiring with the pediatric ward and emergency room teams about any patients admitted with respiratory tract infections (RTIs), including those admitted to the pediatric floor or boarding in the emergency room with admission orders. When a potentially eligible patient is identified, a member of the clinical care team will first approach the parents to inquire if they are willing to be contacted by the research team. If they accept, the research team will approach the family to obtain oral consent to access and review the child's medical records. This oral consent will encompass an explanation of the study's purpose, screening procedures, potential risks and benefits, and measures to ensure confidentiality. Following oral consent, the research team will review the patient's EPIC chart to confirm eligibility based on inclusion and exclusion criteria. If the patient meets the criteria, the research team will provide a detailed explanation of the study to the parents or guardians, obtain written informed consent for participation, and request permission to contact them by telephone for follow-up or potential future studies. Once a patient is deemed eligible for the study, the PI will inform the primary treating physician about the planned enrollment. Following enrollment, the PI will provide the physician with the patient's study allocation, as well as the results of the lung ultrasound, including the impression of whether the respiratory tract infection is likely viral or bacterial.

The screening and enrollment process will continue until the target sample size of 176 patients is achieved, with an estimated enrollment period of 18 months. This comprehensive process ensures efficient identification of eligible participants while maintaining clear communication and collaboration with the treating physicians and families.

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation

16. a- Participants will be randomly assigned to either control (SLUS) or experimental (LUS) group with a 1:1 allocation as per a computer generated Permuted-Block Randomization blocks of size 2 and 4. Ali Hijazi will be responsible for the randomization sequence and giving the allocation by phone and will have no role in outcome assessment and data analysis.

Allocation concealment mechanism

16. b- Allocation concealment will be ensured, as the randomization code will not be released by Ali Hijazi until the patient has been enrolled in the trial.

Implementation

16. c- The randomization process will be conducted by the Co-I J.A., who is not involved in patient recruitment. She will generate the randomization sequence. Once an eligible patient provides consent to participate in the study, the PI will contact J.A. by phone and provide her with the patient's ID number. J.A. will record this information and provide the randomization allocation in return.

Blinding (masking)

17. a- The participants and their parents will be kept unaware of the treatment allocation in order to maintain blinding. The PI and the treating physician will not be blinded to the allocation. To ensure unbiased data analysis, a research assistant who is not part of the research team will input data into separate datasheets on the computer. This will allow the researchers (except AI and JA) to analyze the data without having access to information regarding the treatment allocation. Consequently, the analyst will remain unaware of the study group to which the trial participants have been assigned. Additionally, to maintain independence between lung ultrasound (LUS) and chest X-ray (CXR), the PI will also be blinded to the CXR findings. This approach aligns with the existing literature, which supports LUS as a replacement for CXR in children with lower respiratory tract infections (LRTIs).

Emergency unblinding

17. b- Since the PI and treating physicians will not be blinded to the allocation of patients, any code breaks will not have an impact on the subsequent management of the patients. As a result, there will be no need for exceptional circumstances that would require emergency unblinding.

Methods: Data collection, management, and analysis

Data collection methods

18. a-Outcomes and procedures:

Principal Investigator (PI) Responsibilities and Equipment:
The PI (A.I.) will perform LUS examination within 24 hours of enrollment using the CX50 portable ultrasound machine, manufactured by Philips – Bothell, USA. The machine, owned by the Department of Pediatrics and Adolescent Medicine, will be equipped with a Linear transducer (L:12-3) set to lung presetting. LUS will be conducted exclusively by the PI, who has over five years of credentialing experience in LUS.

Scanning Procedure:

Each lung will be scanned in the longitudinal and transverse orientation from the apex to the diaphragm along three lines: the midclavicular line (anterior view), the line between the paraspinal and scapular lines (posterior view), and the mid-axillary line (lateral view), following the methodology described by Copetti and Cattarossi.[21] Both upper and lower lung zones will be examined in each orientation, as shown in Appendix-I. Lung ultrasound score will be calculated based on appendix-III. All captured perspectives will be saved, with each recorded video clip lasting 8 seconds.

Clinical Evaluation and Categorization:

The PI will evaluate patients' clinical findings, including their medical history, physical examination results, and laboratory data to determine the clinical etiology of respiratory symptoms. Patients will be categorized as either having infectious (e.g. patients with fever, cough, positive rapid antigen test or PCR for respiratory infection) or non-infectious etiologies (e.g. patients with a history of chest trauma or asthma), as detailed in Appendix-II A and B. Subsequently, the PI will conduct lung ultrasound scans, and integrate lung ultrasound findings with clinical and laboratory data to suggest an etiology diagnosis targeting a better therapeutic decision.[20]

Infectious Etiology:

For suspected infectious etiologies, patients will be further assessed as clinically stable or unstable (Appendix-II A). Clinically stable conditions are defined by hemodynamic stability without dependence on inotropic and vasopressor support, and not classified under severe pediatric acute respiratory distress syndrome (PARDS) or severe possible PARDS according to the Second Pediatric Acute Lung Injury Consensus Conference (PALICC-2) guidelines with SF ratio > 150 and/or PF ratio > 100.[24] Patients who are clinically unstable will be excluded from the study as they will receive treatment in the pediatric intensive care unit and likely be administered antibiotics for potential bacterial infection. For patients who will be clinically stable and have a potential lower respiratory tract infection, the initial step in LUS involves checking for the presence of B-lines.

If B-lines are absent and there is no consolidation, the condition will be considered as an upper respiratory tract infection (URTI).[25,26]

<u>Bilateral B-lines</u>:

When bilateral B-lines are observed, with or without consolidation smaller than 1 cm, this will be considered viral changes. The diagnosis that will be suggested to the treating physician will be either bronchiolitis (for those under 2 years of age) or viral bronchitis (for those over 2 years of age).[10,14,27,28]

Although a consolidation size of ≥1 cm on LUS typically indicates bacterial pneumonia, a diagnosis of viral pneumonia will still be considered in patients who also exhibit bilateral B-lines.[14,15] In those patients, the next step is to assess for signs of ill appearance or complicated pneumonia (simple or complex pleural effusion, abscess). If such signs are present, bacterial pneumonia will be considered. If these signs are absent, viral pneumonia will be considered,

and a repeat LUS within 48 hours will be advised if clinically indicated. If the follow-up ultrasound shows worsening, bacterial pneumonia will be considered; if there is no change or improvement without antibiotics, this will be considered as viral pneumonia.

Unilateral B-lines:

In cases where B-lines are focal and unilateral with a consolidation ≥1 cm, with or without pleural effusion, and accompanied by a dynamic air bronchogram, bacterial pneumonia will be considered.[29] If the bronchogram is static or absent (hepatization), the etiology may be bacterial pneumonia or atelectasis.[10,15,29,30] When B-lines are focal and unilateral without consolidation, or if accompanied by a consolidation smaller than 1 cm, this will be considered as mild viral infection in most cases, or early bacterial infection. In such cases, a repeat ultrasound within 48 hours will be advised. If the findings show progression to bilateral B-lines, or show improvement without antibiotics, viral etiology will be considered. Conversely, if the findings show consolidation of 1 cm or larger, this will be considered as bacterial pneumonia. Clinically unstable patients and those diagnosed with bacterial pneumonia, superimposed bacterial pneumonia, or complicated pneumonia will be ultimately considered for antibiotic treatment.

Non-infectious etiology:

Patients with suspected non-infectious etiology (Appendix-II B) can present with a range of conditions, such as atelectasis, contusion, cardiogenic edema, pulmonary embolism, chronic lung disease, or lung mass. Our trial will only include patients with LRTIs. Asthma exacerbation can be infection-induced or allergen-induced, thus our trial will include patients with asthma exacerbation. For patients presenting with clinical signs indicative of asthma—such as a past medical history of asthma, acute onset of shortness of breath, and wheezing observed during physical examination—ultrasound findings can be diverse. These may range from normal appearances to the presence of consolidation of any size, B-lines, or pleural effusion.[31] If the consolidation is less than 1 cm, the etiology diagnosis will be considered as asthma exacerbation. This will also be considered in the case of consolidation equal to or larger than 1 cm, with or without static air bronchograms, though a repeat ultrasound within 48 hours will be advised if clinically indicated. Should the repeat ultrasound show that the consolidation is improving without antibiotic treatment, the diagnosis of asthma exacerbation will be considered. Conversely, if LUS findings show worsening, it will be considered as possible superimposed infection. Regarding pleural effusion in patients with a clinical diagnosis of asthma exacerbation, a large or moderate effusion will be considered as bacterial infection. In the case of a small pleural effusion and clinical findings of asthma, a follow-up lung ultrasound within 48 hours will be advised. If the effusion is unchanged or improving without antibiotics, asthma exacerbation will be considered. However, if the effusion worsens, then superimposed bacterial pneumonia will be considered.

Communication and Documentation:

Etiology diagnosis will be communicated to the treating physician to guide treatment decisions. Clinical findings, ultrasound findings and etiology diagnosis will be recorded on a data collection form (Appendix-III). Following the patient's discharge, outcome forms will be filled out, with follow-up phone calls at 1, 2, 3, and 4 weeks post-enrollment to collect data on length of stay, PICU admissions, chest tube insertions, mortality, antibiotic intake, and readmission rates, as well as the type and duration of antibiotics used and the number of CXRs performed during the study period (Appendix-IV).the outcome forms will be filled, along with phone calls at 1, 2, 3 and 4 weeks after enrollment (Appendix-IV).

b- After a participant is enrolled or randomized, the study site will make all reasonable attempts to ensure that the participant is followed throughout the entire study duration. The anticipated rate of loss-to-follow-up is expected to be no more than 5%. The staff at the study site have the responsibility of creating and implementing local standard operating procedures to achieve this level of follow-up.

Data management

19- LUS will be performed twice on each patient during their hospital stay to monitor the progression or regression of LRTI and to screen for signs of complicated pneumonia. Ultrasound findings and etiology diagnoses will be recorded on a data collection form immediately after each LUS exam (see Appendix-III). Socio-demographic data, including age, gender, daycare/school attendance, comorbidities, parental highest level of education, number of siblings, parental smoking habits, and history of breastfeeding, will be directly collected from patients' families.
Primary and secondary outcomes forms will be completed after the patient's discharge from the hospital and during follow-up phone calls at 1 week, 2 weeks, 3 weeks, and 4 weeks post-enrollment (see Appendix-IV). All data retrieved from Appendices III and IV will be entered into REDCap, a web-based application designed specifically for data capture in research studies. This platform ensures secure and reliable data management, facilitating real-time data entry validation and comprehensive data analysis capabilities.
Access to redcap will be password protected, with access restricted to the team of the study.

The integrity of data analysis will be further ensured by the biostatistician collaborator(Z.M.), who will conduct the statistical analysis using data files exported from REDCap, with coded allocations ("A" for SLUS and "B" for LUS arms).
All informed consent, data collection forms, and outcomes forms will be stored in locked cabinets in the principal investigator's (AI) office, with restricted access limited to authorized personnel. Electronic data will be securely stored on the principal investigator's computer, which is password-protected.

Physical data collection forms will be destroyed 10 years after the publication of the study's findings. Data cleaning will be addressed through:

- Requesting missing information during the phone calls after discharge,
- Removing data points that are missing at random if they constitute less than 5% of the data, otherwise using imputation methods (mean or median),
- Performing sensitivity analysis to assess the impact of missing data,
- Documenting all data cleaning procedures thoroughly.

This protocol ensures meticulous management and preservation of data integrity throughout the study.

Statistical methods

20a- Demographic and clinical characteristics variables will be summarized using means and standard deviations for numeric variables, and frequency distribution for the categorical variables. Those characteristics will be checked visually for any sizable imbalances. The primary analysis will include comparing the primary outcome, the rate of antibiotic prescriptions, between the two study arms using the Chi-square test and the univariate logistic regression will be used to obtain the unadjusted odds ratio (OR) and the 95% confidence interval (CI). In addition, adjusted standard error for cluster effect and relative risk (RR) and relative risk reduction (RRR) will be computed with 95% CI. For the secondary analysis, we will adjust the primary analysis based on the imbalances in the demographic variables using multivariate logistic regression and obtain OR and 95% CI. Length of stay in the hospital and frequency of CXR performance by 4 weeks after enrollment are numeric secondary variables. Those will be compared using t-test and univariate and multivariate linear regression. We will report the unadjusted and the adjusted mean differences (slopes) and 95% CI. Rate of chest tube insertion, mortality rate, rate of antibiotic intake and rate of readmission to the hospital both evaluated four weeks following enrollment are categorical secondary outcomes and will be analyzed using the Chi-square test and the univariate and multivariate logistic regression to obtain the unadjusted and adjusted OR and the 95% CI. The analysis will be conducted using the latest version of SPSS. Two-sided p-values with an alpha level of ≤ 0.05 will be used for all tests. The analyses will be conducted by a professional academic statistician who will be blinded to the study groups. Table 4 summarizes the statistical tests for each outcome.

Variable	Type	unadjusted (95% CI)	Adjusted (95% CI)	RR (95% CI)	RRR (95% CI)

Rate of antibiotic prescriptions upon discharge	Categorical	✓	OR	✓ OR	SE	✓	✓
Length of Stay	Numeric	✓	β_1	✓	β_1		
Frequency of CXR	Numeric	✓	β_1	✓	β_1		
Rate of chest tube insertion	Categorical	✓	OR	✓	OR		
Mortality rate	Categorical	✓	OR	✓	OR		
Rate of antibiotic intake and rate of readmission to the hospital both evaluated 4 weeks following enrollment	Categorical	✓	OR	✓	OR		

Table 4: summary of statistical tests for each outcome

20b- We are not going to conduct a subgroup analysis.

20c- We will perform intention-to-treat analysis to examine the effectiveness of LUS usage compared to SLUS. The potential impact of missing data on the results will be evaluated through measuring means or medians.

Methods: Monitoring

Data monitoring

21- a- A Data and Safety Monitoring Committee (DSMC) will be formed, operating independently from the study organizers. Throughout the recruitment phase of the study, the DSMC will receive one interim analysis, which will be treated as confidential. Additionally, the committee may request any other analyses as deemed necessary. The main function of the DSMC is to regularly assess the accumulating data and make decisions regarding potential modifications or discontinuation of the trial. The DSMC will communicate the results of its evaluations to the trial steering committee.
The chair of the DSMC is going to be Dr. Mona Nabulsi (Pediatrician, Department of Pediatrics and Adolescent Medicine, AUBMC) with two members: Dr. Lama Charafeddine (Neonatologist, Department of Pediatrics and Adolescent Medicine, AUBMC), and Dr. Hani Tamim (Biostatistician, Clinical Research Institute, AUB). All members are at the professorial rank. The charter will be appended to the protocol (Appendix V).

21b- An interim analysis will be conducted on the primary endpoint once during the trial, once 50% of the patients have been randomized and completed the 4-week follow-up. The analysis will be carried out by the Collaborator (Z.M.), who will be unaware of the patients' allocation. The statistician will provide a report to DSMC. The DSMC will have full access to unblinded data and will hold a joint meeting with the steering committee to discuss the results of the interim analysis. The steering committee will make the decision regarding the continuation of the trial. For the interim analysis, the Peto approach will be utilized, employing symmetric stopping boundaries at a significance level of $P < 0.01$.

Harms

22- Lung ultrasonography is a radiation-free imaging technique, making it a safe choice for children. There will be no harm induced to patients from the intervention itself. We will still capture solicited and unsolicited adverse events and report it to IRB. As for the potential complications of LRTIs (ICU admission, chest tube, mortality, readmission to the hospital) that can occur in both study arms, this can occur in those patients who will not receive a timely etiology treatment, in particular antibiotics in the case of bacterial pneumonia. Complications of mismanagement of LRTIs and the rate of antibiotic intake and rate of CXR performed by 4 weeks after enrollment will be assessed as secondary endpoints.

Recognizing the potential for false negatives with lung ultrasound, it's important to highlight that all patients will receive the standard of care, which includes cessation of antibiotics when clinical judgment and diagnostic findings, such as CXR and lab results, indicate a viral infection. This practice is consistent with our institution's approach, even in the vulnerable 3 to 6 months age group. The literature supports LUS as having superior sensitivity compared to CXR, minimizing the risk associated with false negatives. Additionally, the ongoing observation of admitted patients and repeated ultrasound before discharge provide further safeguards. These measures ensure that any necessary adjustments to treatment can be made timely based on the treating physician's continuous assessment.

Auditing

23- The investigators will handle the data in accordance with standard confidentiality regulations. Direct access to source documents will be granted for monitoring, audits, and inspections. IRB will conduct audits on an annual basis. Moreover, the study protocol will be published before starting the recruitment of participants.

Ethics and dissemination

Research ethics approval

24- The institutional review board (IRB) at AUB will review and approve the protocol and informed consent forms and the supplementary appendices. This review ensures that the documents meet scientific standards and comply with relevant regulations concerning research and the protection of human subjects. Once the initial review and approval are complete, the IRBs will continue to periodically review the consent process and protocol-related issues, such as recruitment and the criteria for including or excluding participants. These reviews will occur at least once every year. Additionally, the PI will provide safety and progress reports to the IRBs at least once a year as part of continuing review.

Protocol amendments

25- If any changes to the protocol could affect how the study is conducted, the potential benefits for patients, or patient safety, including modifications to study objectives, design, patient population, sample sizes, study procedures, or significant administrative aspects, a formal amendment to the protocol will be necessary. This amendment must be submitted to the IRB for approval before it can be implemented. On the other hand, administrative changes to the protocol refer to minor corrections or clarifications that do not impact the study's conduct. The IRB will be informed of any administrative changes that occur.

Consent or assent

26- a- All members of the research team will receive training on the process of obtaining informed consent from parents who are 18 years old, as well as assent from participants aged 7 to 17 years. The team member will ensure that participants and their parents are fully introduced to and comprehensively informed about the research study. Written consent and assent will be obtained from them. Signed consent forms will be provided to all parents involved in the trial, and these forms will be available in both English and Arabic languages.

b- Written consent and assent will be obtained from parents and their children, allowing their participation in the current study, as well as granting permission to be contacted by telephone for further follow-up if necessary or for future relevant studies.

Confidentiality

27- We aim to maintain the highest standards of confidentiality and security for the data collected in this study.
Access to the REDCap project will be restricted to authorized personnel only. Users will require login credentials and will be assigned roles based on their need to access specific data. All data

collected will be stored on Redcap's secure servers, ensuring compliance with institutional and federal regulations for data protection and confidentiality. All research team members will undergo training on data security and confidentiality practices to ensure they understand their responsibilities in protecting participant information. Additionally, the data will be stored in a password-protected folder on the desktops of the Principal Investigator, Dr. Ali Ismail.
All informed consent and data collection forms will be securely stored in locked cabinets located in the principal investigator's (AI) office. Access to these cabinets will be restricted to the principal investigator and research assistant. All data collection forms will be destroyed after a period of 10 years from the publication of the study's findings.

Declaration of interests

28- The principal investigator (AI) will have no conflict of interest for the overall trial.

Access to data

29- The final dataset, which will be password protected, will be accessible only to the Principal Investigator (AI). In order to maintain confidentiality, any data shared with other members of the project team will be stripped of any identifying participant information.

Ancillary and post-trial care

30- Ultrasound does not cause any harm or risk on our study patients' health. That's why patients that will be enrolled into the study will not be candidates to be covered by insurance or indemnity for harm.

Dissemination policy

31- a- Maintaining the scientific integrity of the project is crucial, and therefore the data will be analyzed and reported on a study-wide basis. The Steering Committee will provide guidance on the timing and venues for presenting such endpoint data. The planned duration of the PLUS-AP project is 1.5 years till the randomization of the last participant, but it may end earlier or later depending on circumstances. We will strive to minimize the time between the completion of data collection and the release of study results. It is anticipated that it will take approximately 6-12 months to compile the final results paper for submission to an appropriate journal. The study results will be shared with participating physicians, referring physicians, patients, as well as through poster presentation and oral presentation at meetings.
b- The final authority over the content of manuscripts submitted for publication will be given to individuals who meet the authorship criteria defined by the International Committee of Medical

Journal Editors.[32] Professional medical writers will not be engaged or hired for the purpose of manuscript development.

c- Within a maximum of 3 years after collecting the post-randomization data, when an external team requests access to data, they usually submit a research question along with an analysis plan. The Trial Steering Committee reviews this submission and either approves it or requests clarifications. Upon approval, the external team has the option to work independently of the trial TSC or collaborate with them.

Appendices

Informed consent materials

32- Appendix VI

Biological specimens

Not Applicable

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Appendix I: Illustration of Pediatric Lung Ultrasound Approaches

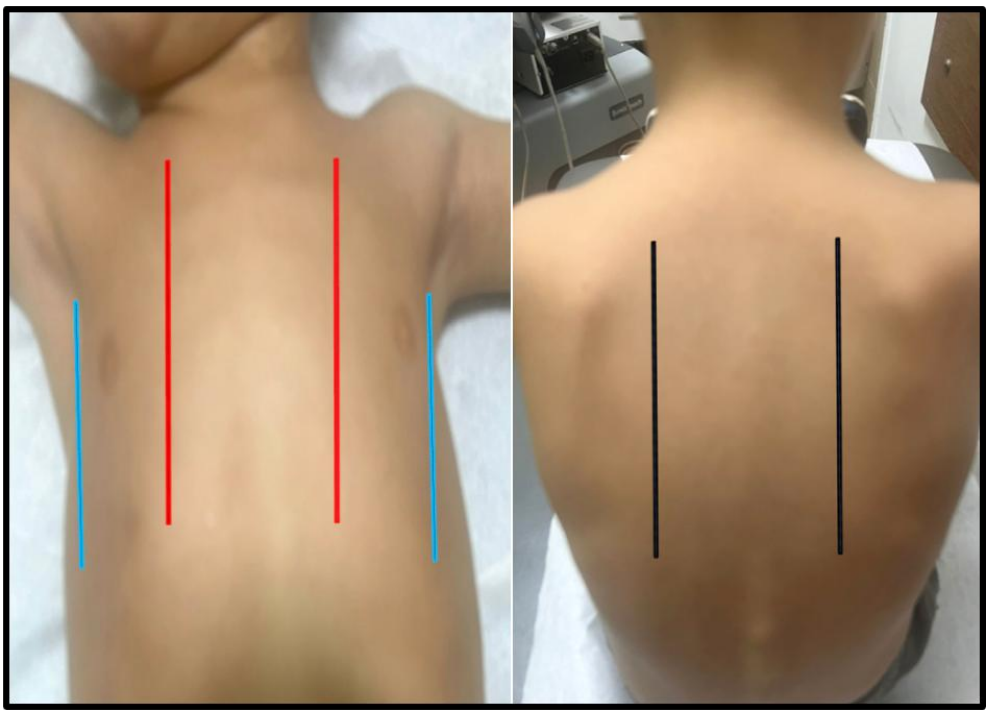
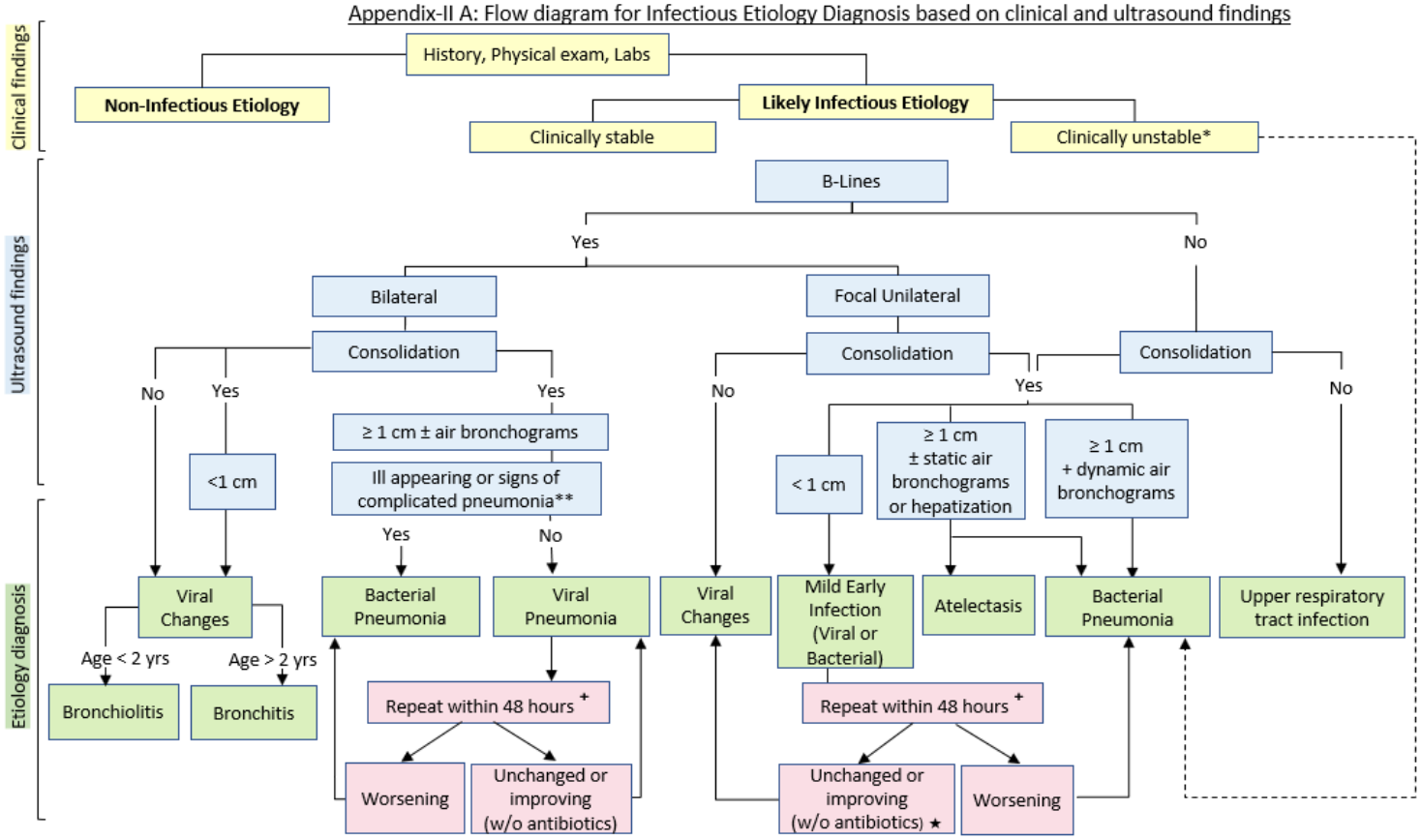


Illustration of Pediatric Lung Ultrasound Approaches

In red: Anterior Approach: Midclavicular lines
In blue: Lateral Approach: Midaxillary lines
In black: Posterior Approach: the Vertical lines extending between the paraspinal and scapular lines.
Reference: (21)

Appendix-II A: Flow diagram for Infectious Etiology Diagnosis based on clinical and ultrasound findings



Labs: Laboratory findings, Yrs: years, w/: with, w/o: without

* Clinically unstable patients are treated presumptively for bacterial pneumonia

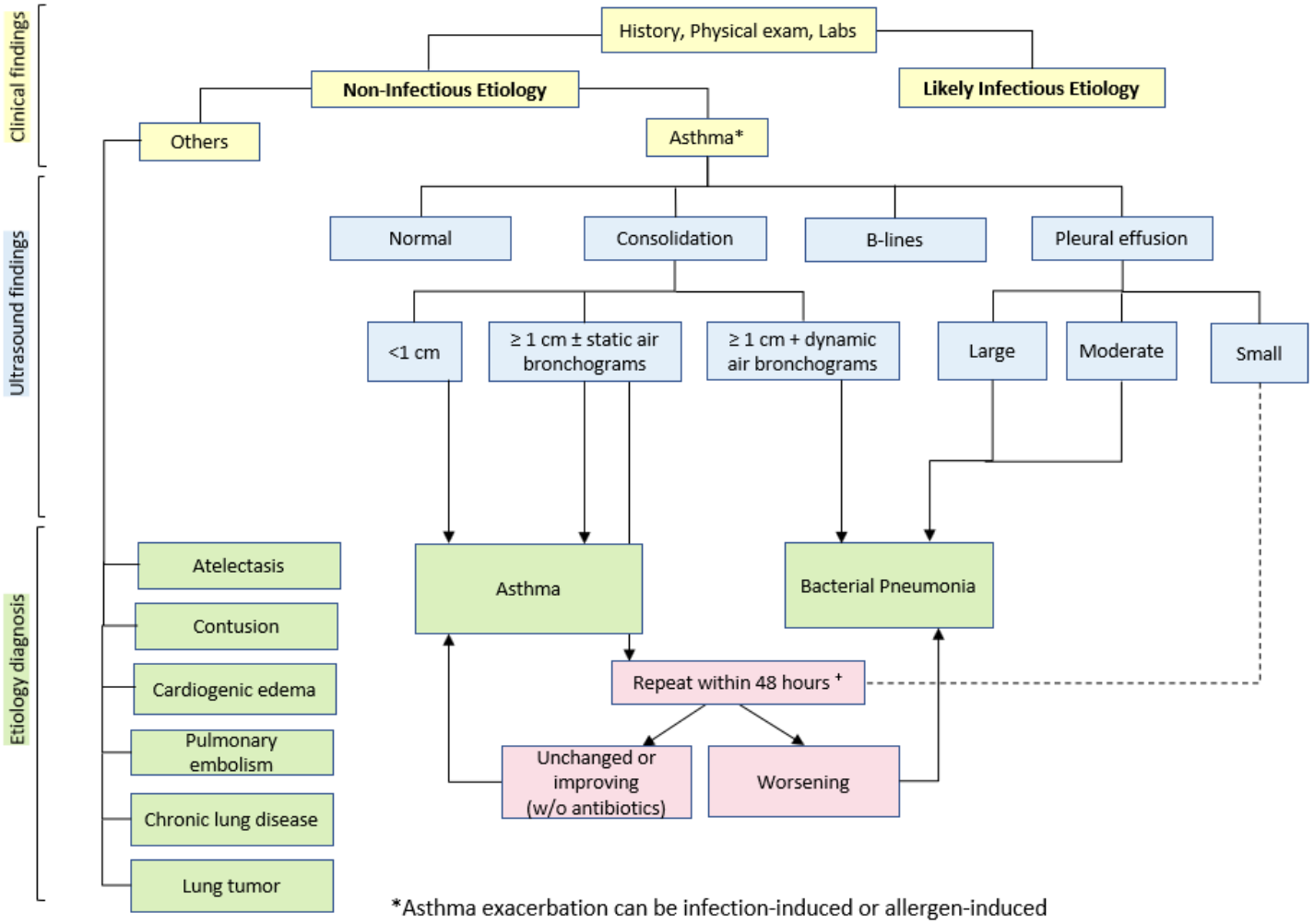
** Signs of complicated pneumonia: simple or complex pleural effusion, abscess

+ If clinically indicated

★ If B-lines become bilateral, refer to the section of the diagram with bilateral B-lines

References: (10,14,15,24-30)

Appendix-II B: Flow diagram for Non-Infectious Etiology Diagnosis based on clinical and ultrasound findings



*Asthma exacerbation can be infection-induced or allergen-induced

+ If clinically indicated

Reference: (31)

Appendix III: Data Collection Form (PLUS-AP trial)

1- Demographics:

Age: Gender: Location: Daycare/School:

Comorbidities: Parents highest level of education: Number of siblings:

Parental smoking: History of breastfeeding:

2- Vital signs: Temp: HR: RR: BP: SpO2:

On oxygen supplementation? Yes / No if Yes, Specify: _____

3- Respiratory Symptoms:

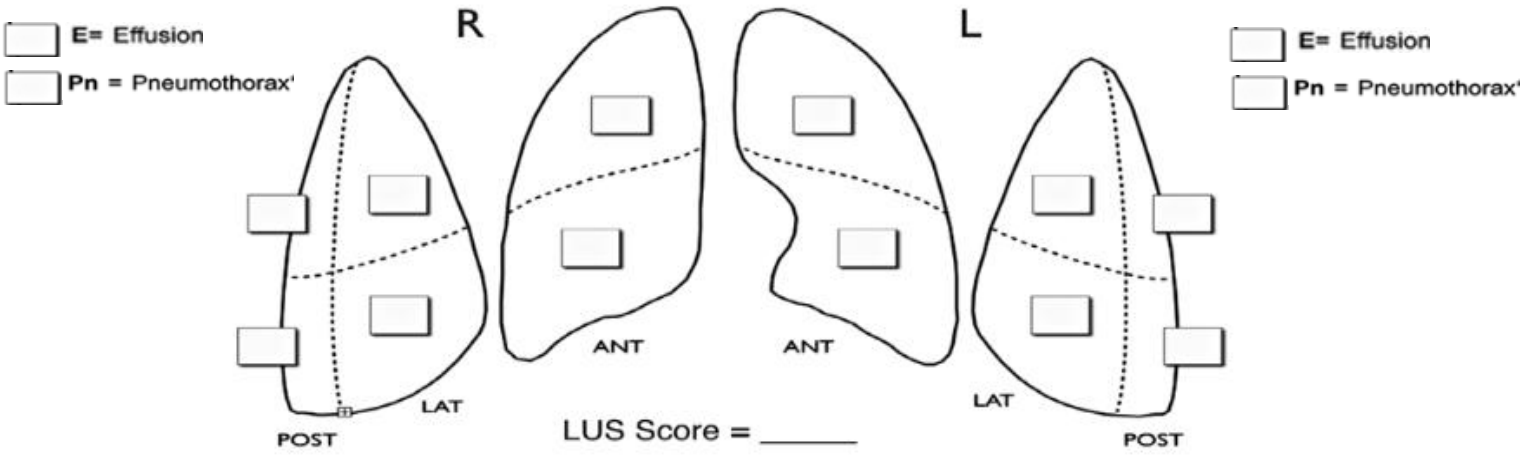
- Respiratory distress
- Cough
- Fever
- Chest pain
- Pleuritic Chest pain
- Blunt trauma
- Penetrating Trauma
- Other:

4- Lab Results:

5-Views:

Right Anterior Thorax:	□ Adequate	□ Limited	□ Not obtained
Right Lateral Thorax:	□ Adequate	□ Limited	□ Not obtained
Right Posterior Thorax:	□ Adequate	□ Limited	□ Not obtained
Left Anterior Thorax:	□ Adequate	□ Limited	□ Not obtained
Letf Lateral Thorax:	□ Adequate	□ Limited	□ Not obtained
Left Posterior Thorax:	□ Adequate	□ Limited	□ Not obtained

Lung Ultrasound Score:



A 0- to 3-point score is given to each zone as follows:

0: Presence of A-lines ∓ < 3 discrete B lines in 1 view;

1: Presence of ≥ 3 discrete B-lines in one view;

2: Presence of confluent B-Lines with or without subcentimetric subpleural consolidations

3: Presence of extended consolidations (≥ 1cm)

6- LUS Findings:

Right Lung Sliding:

• Present • Absent • Indeterminate

Right Lung Point:

• Absent • Present • Indeterminate

Left Lung Sliding:

• Present • Absent • Indeterminate

Left Lung Point:

• Absent • Present • Indeterminate

Right B-Lines:

• Absent • Focal • Bilateral • Anterior • Lateral • Posterior

Right Consolidation:

• Absent • <1 cm (Ant, Lat, Post) • ≥1 cm (Ant, Lat, Post) • Air bronchograms

Right Pleural Effusion:

• Absent • Simple • Complex • Mild • Moderate • Severe

Left B-Lines:

• Absent • Focal • Bilateral • Anterior • Lateral • Posterior

Left Consolidation:

• Absent • <1 cm (Ant, Lat, Post) • ≥1 cm (Ant, Lat, Post) • Air bronchograms

Left Pleural Effusion:

• Absent • Simple • Complex • Mild • Moderate • Severe

Comments: _____

7- LUS Etiology Diagnosis:

• URTI • Viral Infection (Bronchiolitis/Bronchitis) • Viral Pneumonia • Bacterial Pneumonia

• Superimposed bacterial pneumonia •Complicated pneumonia (effusion, abscess) • Asthma

• Mild Early Infection

• Other: _____

8-Duration of Ultrasound: Time started: Time completed:

9-Recommendation: _____

Appendix IV: Outcomes

Length of stay:

PICU admission:

- o Yes
- o No

Chest tube insertion:

- o Yes
- o No

Mortality:

- o Yes
- o No

	Antibiotic Prescription/intake	Date	Antibiotic type/Duration	№ of CXR done	Readmission
Discharge					
Phone call at 1 week					
Phone call at 2 weeks					
Phone call at 3 weeks					
Phone call at 4 weeks					

Conclusion: