

**RESPIRATORY CARE****Computerized adventitious respiratory sounds as outcome measures for respiratory therapy: a systematic review**

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1 **TITLE:**

2 **Computerized adventitious respiratory sounds as outcome measures for respiratory**  
3 **therapy: a systematic review**

4 **ARS as outcome measures for respiratory therapy**

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16 The authors report no conflict of interests.

17 **Contributors**

18 AO conducted the literature search. AM, AO and CJ decided the articles inclusion. AM and AO  
19 assessed the studies quality. AM and CJ extracted the data from studies. **AM, CJ and AO**  
20 **drafted the manuscript and revised it critically for important intellectual content.**

21

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1 **Abstract**

2 **Introduction:** There is a need to develop simple, non-invasive and sensitive outcome measures  
3 for respiratory therapy. Adventitious respiratory sounds (i.e., crackles and wheezes) can be  
4 objectively characterized with computerized respiratory sound analysis and have been shown to  
5 contribute for diagnosis purposes however; their potential to be used as outcome measures is  
6 unknown. Thus, this systematic review synthesizes the evidence on the use of computerized  
7 adventitious respiratory sounds as outcome measures.

8 **Methods:** The Web of knowledge, MEDLINE, EMBASE and SCOPUS databases were  
9 searched. Reviewers independently selected studies according to the eligibility criteria. Effect  
10 sizes and 95% confidence intervals were computed.

11 **Results:** Twelve studies with different designs (observational (n=3), quasi-experimental (n=7)  
12 and randomized controlled trial (n=2)) were included. Eight studies were conducted with adults  
13 and four with children. Most studies explored only one type of adventitious respiratory sound.  
14 For wheezes, the occupation rate seemed to be the most promising parameter to be used as an  
15 outcome measure, with high/medium effect sizes (from 0.62 to 1.82). For crackles, the largest  
16 deflection width showed high effect sizes (1.31 and 1.04) however, it was only explored in one  
17 study. Crackle number and two cycle duration presented conflicting information, with high/poor  
18 effect sizes depending on the study.

19 **Conclusion:** Specific variables of each adventitious respiratory sound detected and  
20 characterized by computerized respiratory sound analysis showed high effect sizes and thus,  
21 potential to be used as outcome measures. Further research with robust study designs, larger  
22 samples, both of children and adult populations, and following CORSA guidelines are needed to  
23 build evidence base knowledge on this topic.

24 Key words: computerized respiratory sound analysis; respiratory sounds; adventitious  
25 respiratory sounds; wheezes; crackles; outcome measure

## 1 Introduction

2 Respiratory diseases are a major cause of societal, health and economic burden worldwide<sup>1</sup>.  
3 Therefore, in the last decade, significant research efforts have been dedicated to improve early  
4 diagnosis and routine monitoring of patients with respiratory diseases to allow timely  
5 interventions. However, this has been found to be highly challenging with the available  
6 respiratory measures (e.g., spirometry, blood gas analysis, imaging techniques), since they are  
7 commonly affected by patient's motivation and cooperation, are not always available in all  
8 clinical settings and are expensive<sup>2,3</sup>.

9 Computerized respiratory sound analysis, which consists of recording patients' respiratory  
10 sounds with an electronic device and analyzing them based on specific signal characteristics, is  
11 a simple, objective and non-invasive method to detect and characterize adventitious respiratory  
12 sounds (ARS), i.e., crackle (CR) and wheeze (WH). ARS provide crucial information on  
13 respiratory dysfunction<sup>4</sup> and changes in their characteristics (intensity, duration, timing, etc.)  
14 might inform the clinical course of respiratory diseases and treatments<sup>5,6</sup>. Through the use of  
15 computerized respiratory sound analysis, ARS have been found to be a more sensitive  
16 indicator, detecting and characterizing the severity of the respiratory disease before any other  
17 measure<sup>7</sup>. Thus, this approach through the objective data collection and management,  
18 generation of permanent records of the measurements made with easy retrievability and  
19 through graphical representations, assists the diagnosis and monitoring of patients with  
20 respiratory diseases<sup>8-11</sup>.

21 However, research on this topic has been focusing on the use of computerized respiratory  
22 sound analysis as a diagnostic aid<sup>12</sup> and the findings reporting its potential to be used as an  
23 outcome measure, i.e., to monitor respiratory treatments, are widespread in the literature. Thus,  
24 this systematic review synthesizes the evidence on the use of computerized ARS as outcome  
25 measures.

## 26 Methods

### 27 Search strategy

1 An electronic literature search was performed from December 2012 to January 2013 in Web of  
2 knowledge (1970-2012), MEDLINE (1948-2012), EMBASE (1974-2012) and SCOPUS (1960-  
3 2013) databases. Search terms were based on a combination of the following keywords:  
4 monitor\* OR "computerized analyses" OR "digital auscultation" OR "electronic auscultation" OR  
5 "automatic auscultation" OR "acoustic signal processing" AND "added lung sounds" OR  
6 "abnormal lung sounds" OR "adventitious lung sounds" OR "adventitious respiratory sounds"  
7 OR crackle\* OR wheez\*. The search terms were limited to titles and abstracts. The reference  
8 lists of the selected articles were scanned for other potential eligible studies. Additionally, a  
9 weekly update was conducted until June 2013. This systematic review is reported according to  
10 preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines<sup>13</sup>.

### 11 **Eligibility criteria**

12 Articles were included if **1)** they detected and characterized ARS with computerized respiratory  
13 sound analysis before and after an intervention on adults or children; **2)** were experimental,  
14 quasi-experimental or observational studies; **3)** were full papers published as original articles or  
15 in conference proceedings and **4)** were written in English, Portuguese, Spanish or French.  
16 Articles were excluded if the study was conducted with animals or assessed ARS with  
17 computerized respiratory sound analysis only at one specific moment in time. Book chapters,  
18 review papers, abstracts of communications or meetings, letters to the editor, commentaries to  
19 articles, unpublished work and study protocols were not considered suitable and, therefore,  
20 were also excluded from this review.

### 21 **Study selection**

22 Duplicates were first removed. Then, the title, abstract and keywords were analyzed to assess  
23 the type and relevance of the publication for the scope of the review. Finally, the full-text of  
24 potentially relevant articles was independently screened for content by the three reviewers to  
25 decide its inclusion in the review. Reviewers resolved disagreements by consensus.

### 26 **Data extraction**

1 Data from the included articles were extracted in a structured table-format, i.e.,: first author's  
2 last name and year of publication, type of study, participants, intervention, data collection  
3 protocol, recording device, data analyses, ARS outcome and findings.

#### 4 **Quality assessment**

5 The quality of the included studies was assessed with the checklist created by Downs and  
6 Black<sup>14</sup>. The checklist provides a list of 27 questions to measure study quality, split into five  
7 sections: reporting (ten items); external validity (three items); internal validity – bias (seven  
8 items); internal validity – confounding (seven items) and power (one item). Similarly to previous  
9 systematic reviews<sup>15, 16</sup>, the scoring for question 27 - dealing with statistical power, was  
10 simplified to a choice of awarding either 1 point or 0 points, depending on whether there was  
11 sufficient power to detect a clinically important effect. Downs and Black score ranges were  
12 grouped into the following 4 quality levels: excellent (26 –28), good (20 –25), fair (15–19), and  
13 poor ( $\leq 14$ )<sup>15, 16</sup>. The risk of bias assessment was carried out by two independent reviewers.  
14 Disagreements between reviewers were resolved by reaching a consensus through discussion.

#### 15 **Data analysis**

16 To determine the consistency of the quality assessment performed by the two reviewers, an  
17 inter-rater agreement analysis using the Cohen's kappa was performed. The value of Cohen's  
18 kappa ranges from 0 to 1 and can be categorized as slight (0.0-0.20), fair (0.21-0.40), moderate  
19 (0.41-0.60), substantial (0.61-0.80) or almost perfect ( $\geq 0.81$ ) agreement<sup>17</sup>. This statistical  
20 analysis was performed using PASW Statistics (version 18.0, SPSS Inc., Chicago, IL). **When**  
21 **quantitative pooling was appropriate the effect sizes together with the 95% confidence intervals**  
22 **(95% CI) were computed for the outcomes of interest. The effect sizes (ES) were interpreted as**  
23 **low (0.20), medium (0.50) and high (0.80) effect magnitudes<sup>18</sup>. This** quantitative data analyses  
24 were performed using the meta-analysis software Comprehensive Meta-Analysis (CMA) version  
25 2 (Biostat, Englewood, New Jersey)<sup>19</sup>.

## 26 **Results**

### 27 **Study selection**

1 The database search identified 1224 records. After duplicates removal, 900 records were  
2 screened for relevant content. During the title, abstract and keyword screening, 876 articles  
3 were excluded. The full-text of the 24 potentially relevant articles was assessed and 18 articles  
4 were excluded due to the following reasons: ARS detection was performed with standard  
5 auscultation (n=2) or manual annotation (n=4), ARS automatic detection occurred only in one  
6 specific time-point to validate algorithms (n=5), did not provide data on ARS (n=3) and an  
7 intervention was absent (n=4). Six original articles were included in the review. The search for  
8 relevant articles within the reference list of the selected articles retrieved 6 studies which were  
9 also included.

10 *(insert figure 1 about here)*

### 11 **Quality assessment**

12 The articles included in this review scored 10 to 21 on the Downs and Black checklist, with a  
13 mean of 14.42±0.93 (Table 1). Results of the risk of bias assessment indicated that seven  
14 (64%) studies had poor quality, four had fair quality and one good quality. Studies scored  
15 particularly poor on the following items: description of confounders, sample representativeness,  
16 patient blinding, outcome assessor blinding, recruitment, randomization, adjust for confounding  
17 factors in the analysis and power to detect outcomes that are clinically important. The  
18 agreement between two authors was almost perfect (k=0.825; 95% CI 0.758-0.885; p=0.001).

19 *(insert table 1 about here)*

### 20 **Study characteristics**

21 The majority of the included studies were quasi-experimental<sup>5, 20-25</sup>, three were observational<sup>26-28</sup>  
22 and two were randomized controlled trials<sup>29, 30</sup>. Ten studies recruited patients receiving  
23 specialized care and two during hospital admission<sup>24, 27</sup>. A total of 275 subjects (n=126; 45.8%  
24 male) participated in the included studies, 47 were healthy subjects and 208 had respiratory  
25 conditions (Asthma (n=84), Pneumonia (n=11), Cystic fibrosis (n=23), Chronic Obstructive  
26 Pulmonary Disease (COPD) (n=6), prolonged cough (n=28), Bronchiolitis (n=27),  
27 **Bronchiectasis** (n=23) and Lower Respiratory Tract Infection (LRTI) (n=26)). Eight studies were

1 conducted with adults (n=167; 60.7%; age range 21-73 years old)<sup>5, 21, 24-29</sup> and four with children  
2 (n=108; 39.3%; age range 4 months - 18 years old)<sup>20, 22, 23, 30</sup>.

3 The interventions of most studies consisted of pharmacotherapy<sup>20-30</sup>, only two studies combined  
4 pharmacotherapy with respiratory physical therapy<sup>5, 29</sup>. The respiratory physical therapy  
5 consisted mainly in active cycle of breathing techniques<sup>5, 29</sup>, but also breathing retraining  
6 techniques; incentive spirometry; thoracic mobility, expansion and flexibility exercises and  
7 aerobic training<sup>29</sup>. In almost all studies, the respiratory sounds were recorded in more than one  
8 chest location however, in three studies recordings were performed exclusively in the trachea<sup>21,</sup>  
9 <sup>25, 26</sup>. Only the three more recent studies, acquired the respiratory sounds following the  
10 Computerized Respiratory Sound Analysis (CORSA) guidelines for short-term acquisition<sup>5, 28, 29</sup>.  
11 The recording devices used varied among studies: microphones<sup>21, 24, 25, 27, 29</sup>, piezoelectric  
12 sensors<sup>20, 22, 23, 26, 30</sup> and electronic stethoscopes<sup>5, 28</sup>.

13 Algorithms based on Fast Fourier Transformation were the most used to automatically detect  
14 ARS. Two studies used an algorithm based on Short-Time Fourier transformation<sup>28, 29</sup> and one  
15 used a modification of the algorithm proposed by Shabtai-Musih et al.<sup>31</sup> and Homs-Corbera et  
16 al.<sup>25, 32</sup>. A total of nine studies analyzed WHs (3 were conducted in children), two analyzed CRs<sup>5,</sup>  
17 <sup>27</sup> and one both WHs and CRs in children<sup>30</sup>. Two studies detected breathing cycles  
18 automatically, one used an analogous method reported by Qiu et al.<sup>5, 33</sup> and the other used the  
19 Huq and Moussavi algorithm<sup>30, 34</sup>. Only three studies considered the breathing phases  
20 (inspiration and expiration) in the analysis of the ARS<sup>26, 27, 29</sup>.

21 *(insert table 2 about here)*

## 22 **Synthesis of the results**

### 23 **Wheezes**

#### 24 *Presence*

25 The presence of WHs was used to identify a bronchial response during bronchial provocation  
26 tests in two studies conducted with children<sup>20, 22</sup>. Sanchez et al. (1993) used concentrations of



1 methacholine and found that WHs had 50% sensitivity and 100% specificity to detect bronchial  
2 hyperreactivity<sup>20</sup>. Bentur et al. (2004) observed that WHs were detected after a mean adenosine  
3 concentration of 15.6mg/ml<sup>22</sup>. Both studies verified that WHs were feasible to assess bronchial  
4 reactivity.

#### 5 *Number*

6 Two studies investigated the number of WHs in adults. Oliveira et al. (2013) found a significant  
7 increase in the number of WHs after 3 weeks of standard medical treatment (6 vs. 14.8; p=0.03;  
8 ES=4.38) in patients with LRTI<sup>28</sup>. A similar result, but not significant, was found in subjects with  
9 stable asthma after terbutaline inhalation (ES=0.34), however in healthy subjects and subjects  
10 with non-stable asthma a non-significant decrease was observed (ES=-0.10 and ES=-0.012,  
11 respectively)<sup>25</sup>.

#### 12 *Frequency*

13 The frequency of WHs was investigated in four studies conducted with adults<sup>21, 25, 28, 29</sup>. After  
14 terbutaline inhalation, the frequency of WHs significantly decreased in patients with asthma  
15 (ES=-0.15), COPD (ES=-0.21) and in healthy subjects (ES=-0.28)<sup>21</sup>. Similar, however non-  
16 significant, results were found with the same intervention in healthy subjects (ES=-0.18) and  
17 subjects with non-stable asthma (ES=-0.24)<sup>25</sup>. In subjects with stable asthma (ES=0.01)<sup>25</sup> and  
18 LRTI (ES=-0.06)<sup>28</sup> the frequency remained approximately the same. Dinis et al. (2013)  
19 investigated the effect of respiratory physical therapy in subjects with LRTI and observed a non-  
20 significant increase in the frequency of inspiratory and expiratory WHs in both experimental  
21 (ES=0.73 and ES=0.04, respectively) and control groups (ES=0.97 and ES=0.97,  
22 respectively)<sup>29</sup>.

#### 23 *Occupation rate*

24 This parameter, which is the proportion of the respiratory cycle occupied by WHs, was explored  
25 in studies conducted with children and adults. In three studies the wheeze occupation rate  
26 (WH%) was used to analyze the effect of pharmacotherapy<sup>24, 25, 30</sup>. A non-significant reduction in  
27 WH% during the night in the group of subjects administered with long-acting sympathomimetic

1 agent (ES=-1.9) was found; whereas in the placebo group, a significant increase was observed  
2 (ES=1.15)<sup>24</sup>. In a study conducted with infant viral bronchiolitis, WH% also decreased 10  
3 minutes after the administration of epinephrine (ES=-1.09); however it increased in the group of  
4 children administered with albuterol (ES=1.27)<sup>30</sup>. Nevertheless, no significant differences were  
5 found between or within groups. When exploring monophonic and polyphonic WH% significant  
6 change was also not found however, low effect sizes in non-stable and healthy subjects and  
7 medium effect sizes in subjects with stable asthma (ES=-0.54) were found<sup>25</sup>. A significant  
8 decrease in inspiratory and expiratory WH% was found after 3 weeks of pharmacotherapy plus  
9 respiratory physical therapy (ES=-0.66 (inspiratory); ES=-0.64 (expiratory)) or pharmacotherapy  
10 alone (ES=-0.69 (inspiratory); ES=-0.62 (expiratory))<sup>29</sup>. A similar result was found for the  
11 nocturnal WH index, calculated from the WH% (after 2 days (ES=-0.61) and after 6 weeks  
12 (ES=-0.80)), when monitoring respiratory sounds overnight to assess the effects of montelukast  
13 in nocturnal asthma<sup>23</sup>.

#### 14 *Duration*

15 Two studies explored this variable when assessing the impacts of pharmacotherapy with adult  
16 subjects<sup>26, 28</sup>. In both studies WH duration remained approximately the same pre/post  
17 intervention. Only in subjects with moderate and severe obstruction, changes in the duration of  
18 WHs after medication were observed<sup>26</sup>.

#### 19 **Crackles**

##### 20 *Number*

21 Three studies analyzed the number of CRs before and after intervention and no significant  
22 differences were found. In two studies, this variable remained approximately the same, with  
23 effect sizes ranging from 0.02 to 0.22<sup>5, 27</sup>. In the study of Beck et al., the number of CRs  
24 increased (ES=0.58) with albuterol and decreased with epinephrine (ES=-1.65)<sup>30</sup>.

##### 25 *Frequency*

1 The **CR** frequency was analyzed only in one study<sup>27</sup>. The **peak frequency** increased during  
2 inspiration (ES=0.11) and decreased during expiration (ES=-0.47) whereas the upper frequency  
3 at -20-dB level decreased in both inspiration (ES=-0.12) and expiration (ES=-0.35). No  
4 significant differences were found.

#### 5 **Two cycle duration (2CD), Largest deflection width (LDW) and Initial deflection width (IDW)**

6 Two studies analyzed the **2CD** variable; Marques et al. did not show any change from pre to  
7 post intervention (ES=0.07)<sup>5</sup> and Piirila showed a non-significant reduction post intervention  
8 both in inspiratory (ES=-0.85) and expiratory (ES=-0.83) phases<sup>27</sup>. In the study of Piirila, both  
9 **LDW** and **IDW** of inspiratory (ES=-1.25 and -0.38) and expiratory (ES=-1 and -0.76) **CRs** were  
10 shorter after the intervention<sup>27</sup>.

#### 11 **Timing**

12 **Only Piirila explored timing parameters of the CRs related to inspiratory tidal volume and**  
13 **inspiratory and expiratory phases. These parameters were significantly different post**  
14 **intervention (ES from 0.5 to 1.14)**

15 **Due to the heterogeneity of the outcome measures used across studies, a meta-analysis was**  
16 **not possible to compute.**

### 17 **Discussion**

18 The main finding of this systematic review was that ARS detected and characterized by  
19 computerized respiratory sound analysis show potential to be used as outcome measures in  
20 children and adults, as specific variables of each ARS presented high effect sizes. However, the  
21 most appropriate variable(s) or variables are yet to be explored.

22 Most studies (11/12) explored **WH** presence and characteristics before/after an intervention.  
23 Wheeze occupation rate seemed to be the most promising parameter to be used as an outcome  
24 measure in children and adults, with medium to high effect sizes varying from 0.62 to 1.9<sup>24, 29</sup>. A  
25 strong association between the proportion of the respiratory cycle occupied by **WHs** and the  
26 degree of bronchial obstruction has been widely demonstrated<sup>21-23, 35</sup>. **This WH parameter, even**

1 when identified with standard auscultation, has shown to be sensitive to assess the  
2 effectiveness of respiratory interventions in children<sup>36, 37</sup>. The WH complexity may also be a  
3 variable of interest as the presence of polyphonic WHs indicates a more serious obstruction  
4 than monophonic WHs<sup>25</sup> however, this was only explored in one study (ES from 0.24 to 0.54)<sup>25</sup>.  
5 Wheeze monitoring has been found to provide more information on the changes of airway  
6 obstruction than measurements of pulmonary function<sup>24</sup>, such as the percentage predicted of  
7 FEV<sub>1</sub> in people with asthma<sup>26</sup>. Thus, WHs and their variables seem to be a promising objective  
8 outcome measure for all populations with a special emphasis on non-collaborative populations  
9 such as children, people with dementia and people in the intensive care. However, it should be  
10 noticed that WHs only occur when there is a flow limitation (but flow limitation is not necessarily  
11 accompanied by WHs), that reaches a critical value, called flutter velocity<sup>38</sup>. Thus, when there is  
12 not enough flow to generate WHs, WHs parameters will not be useful despite the presence of  
13 the respiratory problem. The complementary information provided by CRs is therefore, crucial.

14 Crackles are assumed to be caused by the sudden opening of abnormally closed airways<sup>39-42</sup>,  
15 and their parameters provide essential information about the function and structure of the  
16 tracheobronchial tree<sup>41</sup>, e.g., CR recording during mechanical ventilation has been considered a  
17 simple method to monitor lung recruitment-derecruitment<sup>43</sup>. However, CR variables have been  
18 explored as outcome measures in only three studies<sup>5, 27, 30</sup>. From the limited evidence available,  
19 LDW seemed to be the most valuable parameter to be used as an outcome measure due to its  
20 high effect sizes (1 and 1.25)<sup>27</sup>. Hoevers and Loudon (1990) had already found that LDW  
21 seemed to be a better measure than IDW or 2CD when differentiating between coarse and fine  
22 CRs<sup>44</sup>. However, LDW was also the variable less explored among studies. Conflicting  
23 information was found for the number of CRs and 2CD. The number of CRs had low effect sizes  
24 reported in Piirila (0.14 and 0.22)<sup>27</sup> and in Marques et al. (0.02)<sup>5</sup> studies, and medium/high  
25 effect sizes in Beck et al. (0.74 and 1.65)<sup>30</sup>. High (0.83 and 0.85)<sup>27</sup> and low (0.07)<sup>5</sup> effect sizes  
26 were also found for the variable 2CD. The timing of CRs (ES 0.5 to 1.14) also showed to be  
27 sensitive to the clinical course of pneumonia<sup>27</sup> and has been described as a sensitive  
28 parameter to discriminate respiratory diseases<sup>45</sup>. However, similarly to LDW limited research  
29 has been conducted considering this parameter as an outcome measure. At this point in time it  
30 is difficult to provide any recommendations on which CR's variable(s) are more adequate to be

1 used as an outcome measure to monitor respiratory interventions. These limited and conflicting  
2 data may be a result of the different respiratory sound acquisition sensors (which differ in their  
3 acoustic sensitivity to capture CRs waveforms), filtering and analysis methods used across  
4 studies<sup>46, 47</sup>. Since CRs show potential for diagnosis purposes but also as an outcome measure  
5 for respiratory treatments in different clinical/research contexts, these procedures need to be  
6 standardized. This will allow comparisons among different studies and improve the  
7 understanding of CRs' mechanisms and acoustic characteristics.

8 The study of both main types of ARS is essential to gather complementary information about  
9 the tracheobronchial tree. This information may help health professionals to conduct more  
10 accurate diagnosis and enhance their understanding about the respiratory system responses to  
11 treatments. However, only one study analyzed both types of ARS as an outcome measure in a  
12 study conducted with children<sup>30</sup>. Thus, the study of computerized ARS is an exciting area where  
13 much research is needed to develop knowledge for diagnosis and monitoring of patients but  
14 also to be used as a non-invasive, objective and reliable outcome measure for treatments.

15 The level of evidence that can be drawn at this moment in time from this systematic review is  
16 considerably weak due to the 1) small sample sizes; 2) distinct respiratory therapies and doses  
17 implemented and 3) different ARS variables used in the included studies. The large variety of  
18 acquisition methods used is an issue added to the list of difficulties when comparing results  
19 across studies. A BIOMED 1 Concerted Action project entitled CORSA, funded by the European  
20 Community, developed guidelines for research and clinical practice in the field of respiratory  
21 sound acquisition and analysis<sup>4, 9, 48</sup>. The CORSA project group produced guidelines on the  
22 definitions of medical/technical terms used in pulmonary acoustics; environmental conditions;  
23 patient management procedures; acquisition, pre-processing, digitization and analysis of  
24 respiratory sounds; and also about publishing the results of research<sup>4, 9, 48</sup>. These international  
25 guidelines have been available since 2000, however from the 9 studies conducted after this  
26 year, only 3 followed the acquisition procedures recommended by CORSA. Regarding the  
27 analysis methods, algorithms based on Fast Fourier Transformation were the most used, which  
28 is in accordance with the CORSA recommendations. Future research, with improved study  
29 designs, larger samples, both of children and adult populations, and following the CORSA

1 guidelines, should be conducted to explore the ARS response to respiratory therapies. This will  
2 facilitate the comparison of results from different studies, promote research into the  
3 development of standardized respiratory sound acquisition equipment and analysis and finally  
4 enhance the understanding of computerized ARS as well as their use as an outcome measure.

## 5 **Conclusion**

6 Specific variables of each ARS detected and characterized with computerized respiratory sound  
7 analysis showed high effect sizes and thus may have potential to be an objective, reliable and  
8 non-invasive outcome measure for respiratory therapy in children and adults. Further research  
9 exploring the ARS response to different respiratory therapies are needed to enhance the  
10 understanding of computerized ARS and their clinical use not only for the diagnosis purposes  
11 but also for monitoring patients and treatments.

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- 1 Figure captions
- 2 Figure 1 - PRISMA Flowchart of the included studies.

For Peer Review

1 **TITLE:**

2 **Computerized adventitious respiratory sounds as outcome measures for respiratory**  
3 **therapy: a systematic review**

4 **ARS as outcome measures for respiratory therapy**

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15 **Conflict-of-interest statement**

16 The authors report no conflict of interests.

17 **Contributors**

18 AO conducted the literature search. AM, AO and CJ decided the articles inclusion. AM and AO  
19 assessed the studies quality. AM and CJ extracted the data from studies. AM, CJ and AO  
20 drafted the manuscript and revised it critically for important intellectual content.

21

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1 **Abstract**

2 **Introduction:** There is a need to develop simple, non-invasive and sensitive outcome measures  
3 for respiratory therapy. Adventitious respiratory sounds (i.e., crackles and wheezes) can be  
4 objectively characterized with computerized respiratory sound analysis and have been shown to  
5 contribute for diagnosis purposes however; their potential to be used as outcome measures is  
6 unknown. Thus, this systematic review synthesizes the evidence on the use of computerized  
7 adventitious respiratory sounds as outcome measures.

8 **Methods:** The Web of knowledge, MEDLINE, EMBASE and SCOPUS databases were  
9 searched. Reviewers independently selected studies according to the eligibility criteria. Effect  
10 sizes and 95% confidence intervals were computed.

11 **Results:** Twelve studies with different designs (observational (n=3), quasi-experimental (n=7)  
12 and randomized controlled trial (n=2)) were included. Eight studies were conducted with adults  
13 and four with children. Most studies explored only one type of adventitious respiratory sound.  
14 For wheezes, the occupation rate seemed to be the most promising parameter to be used as an  
15 outcome measure, with high/medium effect sizes (from 0.62 to 1.82). For crackles, the largest  
16 deflection width showed high effect sizes (1.31 and 1.04) however, it was only explored in one  
17 study. Crackle number and two cycle duration presented conflicting information, with high/poor  
18 effect sizes depending on the study.

19 **Conclusion:** Specific variables of each adventitious respiratory sound detected and  
20 characterized by computerized respiratory sound analysis showed high effect sizes and thus,  
21 potential to be used as outcome measures. Further research with robust study designs, larger  
22 samples, both of children and adult populations, and following CORSA guidelines are needed to  
23 build evidence base knowledge on this topic.

24 Key words: computerized respiratory sound analysis; respiratory sounds; adventitious  
25 respiratory sounds; wheezes; crackles; outcome measure

## 1 Introduction

2 Respiratory diseases are a major cause of societal, health and economic burden worldwide<sup>1</sup>.  
3 Therefore, in the last decade, significant research efforts have been dedicated to improve early  
4 diagnosis and routine monitoring of patients with respiratory diseases to allow timely  
5 interventions. However, this has been found to be highly challenging with the available  
6 respiratory measures (e.g., spirometry, blood gas analysis, imaging techniques), since they are  
7 commonly affected by patient's motivation and cooperation, are not always available in all  
8 clinical settings and are expensive<sup>2,3</sup>.

9 Computerized respiratory sound analysis, which consists of recording patients' respiratory  
10 sounds with an electronic device and analyzing them based on specific signal characteristics: is  
11 a simple, objective and non-invasive method to detect and characterize adventitious respiratory  
12 sounds (ARS), i.e., crackle (CR) and wheeze (WH). ARS provide crucial information on  
13 respiratory dysfunction<sup>4</sup> and changes in their characteristics (intensity, duration, timing, etc.)  
14 might inform the clinical course of respiratory diseases and treatments<sup>5,6</sup>. Through the use of  
15 computerized respiratory sound analysis, ARS have been found to be a more sensitive  
16 indicator, detecting and characterizing the severity of the respiratory disease before any other  
17 measure<sup>7</sup>. Thus, this approach through the objective data collection and management,  
18 generation of permanent records of the measurements made with easy retrievability and  
19 through graphical representations, assists the diagnosis and monitoring of patients with  
20 respiratory diseases<sup>8-11</sup>.

21 However, research on this topic has been focusing on the use of computerized respiratory  
22 sound analysis as a diagnostic aid<sup>12</sup> and the findings reporting its potential to be used as an  
23 outcome measure, i.e., to monitor respiratory treatments, are widespread in the literature. Thus,  
24 this systematic review synthesizes the evidence on the use of computerized ARS as outcome  
25 measures.

## 26 Methods

### 27 Search strategy

1 An electronic literature search was performed from December 2012 to January 2013 in Web of  
2 knowledge (1970-2012), MEDLINE (1948-2012), EMBASE (1974-2012) and SCOPUS (1960-  
3 2013) databases. Search terms were based on a combination of the following keywords:  
4 monitor\* OR "computerized analyses" OR "digital auscultation" OR "electronic auscultation" OR  
5 "automatic auscultation" OR "acoustic signal processing" AND "added lung sounds" OR  
6 "abnormal lung sounds" OR "adventitious lung sounds" OR "adventitious respiratory sounds"  
7 OR crackle\* OR wheez\*. The search terms were limited to titles and abstracts. The reference  
8 lists of the selected articles were scanned for other potential eligible studies. Additionally, a  
9 weekly update was conducted until June 2013. This systematic review is reported according to  
10 preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines<sup>13</sup>.

### 11 **Eligibility criteria**

12 Articles were included if 1) they detected and characterized ARS with computerized respiratory  
13 sound analysis before and after an intervention on adults or children; 2) were experimental,  
14 quasi-experimental or observational studies; 3) were full papers published as original articles or  
15 in conference proceedings and 4) were written in English, Portuguese, Spanish or French.  
16 Articles were excluded if the study was conducted with animals or assessed ARS with  
17 computerized respiratory sound analysis only at one specific moment in time. Book chapters,  
18 review papers, abstracts of communications or meetings, letters to the editor, commentaries to  
19 articles, unpublished work and study protocols were not considered suitable and, therefore,  
20 were also excluded from this review.

### 21 **Study selection**

22 Duplicates were first removed. Then, the title, abstract and keywords were analyzed to assess  
23 the type and relevance of the publication for the scope of the review. Finally, the full-text of  
24 potentially relevant articles was independently screened for content by the three reviewers to  
25 decide its inclusion in the review. Reviewers resolved disagreements by consensus.

### 26 **Data extraction**

1 Data from the included articles were extracted in a structured table-format, i.e.,: first author's  
2 last name and year of publication, type of study, participants, intervention, data collection  
3 protocol, recording device, data analyses, ARS outcome and findings.

#### 4 **Quality assessment**

5 The quality of the included studies was assessed with the checklist created by Downs and  
6 Black<sup>14</sup>. The checklist provides a list of 27 questions to measure study quality, split into five  
7 sections: reporting (ten items); external validity (three items); internal validity – bias (seven  
8 items); internal validity – confounding (seven items) and power (one item). Similarly to previous  
9 systematic reviews<sup>15, 16</sup>, the scoring for question 27 - dealing with statistical power, was  
10 simplified to a choice of awarding either 1 point or 0 points, depending on whether there was  
11 sufficient power to detect a clinically important effect. Downs and Black score ranges were  
12 grouped into the following 4 quality levels: excellent (26 –28), good (20 –25), fair (15–19), and  
13 poor ( $\leq 14$ )<sup>15, 16</sup>. The risk of bias assessment was carried out by two independent reviewers.  
14 Disagreements between reviewers were resolved by reaching a consensus through discussion.

#### 15 **Data analysis**

16 To determine the consistency of the quality assessment performed by the two reviewers, an  
17 inter-rater agreement analysis using the Cohen's kappa was performed. The value of Cohen's  
18 kappa ranges from 0 to 1 and can be categorized as slight (0.0-0.20), fair (0.21-0.40), moderate  
19 (0.41-0.60), substantial (0.61-0.80) or almost perfect ( $\geq 0.81$ ) agreement<sup>17</sup>. This statistical  
20 analysis was performed using PASW Statistics (version 18.0, SPSS Inc., Chicago, IL). When  
21 quantitative pooling was appropriate the effect sizes together with the 95% confidence intervals  
22 (95% CI) were computed for the outcomes of interest. The effect sizes (ES) were interpreted as  
23 low (0.20), medium (0.50) and high (0.80) effect magnitudes<sup>18</sup>. This quantitative data analyses  
24 were performed using the meta-analysis software Comprehensive Meta-Analysis (CMA) version  
25 2 (Biostat, Englewood, New Jersey)<sup>19</sup>.

## 26 **Results**

### 27 **Study selection**



1 The database search identified 1224 records. After duplicates removal, 900 records were  
2 screened for relevant content. During the title, abstract and keyword screening, 876 articles  
3 were excluded. The full-text of the 24 potentially relevant articles was assessed and 18 articles  
4 were excluded due to the following reasons: ARS detection was performed with standard  
5 auscultation (n=2) or manual annotation (n=4), ARS automatic detection occurred only in one  
6 specific time-point to validate algorithms (n=5), did not provide data on ARS (n=3) and an  
7 intervention was absent (n=4). Six original articles were included in the review. The search for  
8 relevant articles within the reference list of the selected articles retrieved 6 studies which were  
9 also included.

10 *(insert figure 1 about here)*

### 11 **Quality assessment**

12 The articles included in this review scored 10 to 21 on the Downs and Black checklist, with a  
13 mean of 14.42±0.93 (Table 1). Results of the risk of bias assessment indicated that seven  
14 (64%) studies had poor quality, four had fair quality and one good quality. Studies scored  
15 particularly poor on the following items: description of confounders, sample representativeness,  
16 patient blinding, outcome assessor blinding, recruitment, randomization, adjust for confounding  
17 factors in the analysis and power to detect outcomes that are clinically important. The  
18 agreement between two authors was almost perfect (k=0.825; 95% CI 0.758-0.885; p=0.001).

19 *(insert table 1 about here)*

### 20 **Study characteristics**

21 The majority of the included studies were quasi-experimental<sup>5, 20-25</sup>, three were observational<sup>26-28</sup>  
22 and two were randomized controlled trials<sup>29, 30</sup>. Ten studies recruited patients receiving  
23 specialized care and two during hospital admission<sup>24, 27</sup>. A total of 275 subjects (n=126; 45.8%  
24 male) participated in the included studies, 47 were healthy subjects and 208 had respiratory  
25 conditions (Asthma (n=84), Pneumonia (n=11), Cystic fibrosis (n=23), Chronic Obstructive  
26 Pulmonary Disease (COPD) (n=6), prolonged cough (n=28), Bronchiolitis (n=27),  
27 Bronchiectasis (n=23) and Lower Respiratory Tract Infection (LRTI) (n=26)). Eight studies were

1 conducted with adults (n=167; 60.7%; age range 21-73 years old)<sup>5, 21, 24-29</sup> and four with children  
2 (n=108; 39.3%; age range 4 months - 18 years old)<sup>20, 22, 23, 30</sup>.

3 The interventions of most studies consisted of pharmacotherapy<sup>20-30</sup>, only two studies combined  
4 pharmacotherapy with respiratory physical therapy<sup>5, 29</sup>. The respiratory physical therapy  
5 consisted mainly in active cycle of breathing techniques<sup>5, 29</sup>, but also breathing retraining  
6 techniques; incentive spirometry; thoracic mobility, expansion and flexibility exercises and  
7 aerobic training<sup>29</sup>. In almost all studies, the respiratory sounds were recorded in more than one  
8 chest location however, in three studies recordings were performed exclusively in the trachea<sup>21,</sup>  
9 <sup>25, 26</sup>. Only the three more recent studies, acquired the respiratory sounds following the  
10 Computerized Respiratory Sound Analysis (CORSA) guidelines for short-term acquisition<sup>5, 28, 29</sup>.  
11 The recording devices used varied among studies: microphones<sup>21, 24, 25, 27, 29</sup>, piezoelectric  
12 sensors<sup>20, 22, 23, 26, 30</sup> and electronic stethoscopes<sup>5, 28</sup>.

13 Algorithms based on Fast Fourier Transformation were the most used to automatically detect  
14 ARS. Two studies used an algorithm based on Short-Time Fourier transformation<sup>28, 29</sup> and one  
15 used a modification of the algorithm proposed by Shabtai-Musih et al.<sup>31</sup> and Homs-Corbera et  
16 al.<sup>25, 32</sup>. A total of nine studies analyzed WHs (3 were conducted in children), two analyzed CRs<sup>5,</sup>  
17 <sup>27</sup> and one both WHs and CRs in children<sup>30</sup>. Two studies detected breathing cycles  
18 automatically, one used an analogous method reported by Qiu et al.<sup>5, 33</sup> and the other used the  
19 Huq and Moussavi algorithm<sup>30, 34</sup>. Only three studies considered the breathing phases  
20 (inspiration and expiration) in the analysis of the ARS<sup>26, 27, 29</sup>.

21 *(insert table 2 about here)*

## 22 **Synthesis of the results**

### 23 **Wheezes**

#### 24 *Presence*

25 The presence of WHs was used to identify a bronchial response during bronchial provocation  
26 tests in two studies conducted with children<sup>20, 22</sup>. Sanchez et al. (1993) used concentrations of

1 methacholine and found that WHs had 50% sensitivity and 100% specificity to detect bronchial  
2 hyperreactivity<sup>20</sup>. Bentur et al. (2004) observed that WHs were detected after a mean adenosine  
3 concentration of 15.6mg/ml<sup>22</sup>. Both studies verified that WHs were feasible to assess bronchial  
4 reactivity.

#### 5 *Number*

6 Two studies investigated the number of WHs in adults. Oliveira et al. (2013) found a significant  
7 increase in the number of WHs after 3 weeks of standard medical treatment (6 vs. 14.8; p=0.03;  
8 ES=4.38) in patients with LRTI<sup>28</sup>. A similar result, but not significant, was found in subjects with  
9 stable asthma after terbutaline inhalation (ES=0.34), however in healthy subjects and subjects  
10 with non-stable asthma a non-significant decrease was observed (ES=-0.10 and ES=-0.012,  
11 respectively)<sup>25</sup>.

#### 12 *Frequency*

13 The frequency of WHs was investigated in four studies conducted with adults<sup>21, 25, 28, 29</sup>. After  
14 terbutaline inhalation, the frequency of WHs significantly decreased in patients with asthma  
15 (ES=-0.15), COPD (ES=-0.21) and in healthy subjects (ES=-0.28)<sup>21</sup>. Similar, however non-  
16 significant, results were found with the same intervention in healthy subjects (ES=-0.18) and  
17 subjects with non-stable asthma (ES=-0.24)<sup>25</sup>. In subjects with stable asthma (ES=0.01)<sup>25</sup> and  
18 LRTI (ES=-0.06)<sup>28</sup> the frequency remained approximately the same. Dinis et al. (2013)  
19 investigated the effect of respiratory physical therapy in subjects with LRTI and observed a non-  
20 significant increase in the frequency of inspiratory and expiratory WHs in both experimental  
21 (ES=0.73 and ES=0.04, respectively) and control groups (ES=0.97 and ES=0.97,  
22 respectively)<sup>29</sup>.

#### 23 *Occupation rate*

24 This parameter, which is the proportion of the respiratory cycle occupied by WHs, was explored  
25 in studies conducted with children and adults. In three studies the wheeze occupation rate  
26 (WH%) was used to analyze the effect of pharmacotherapy<sup>24, 25, 30</sup>. A non-significant reduction in  
27 WH% during the night in the group of subjects administered with long-acting sympathomimetic

1 agent (ES=-1.9) was found; whereas in the placebo group, a significant increase was observed  
2 (ES=1.15)<sup>24</sup>. In a study conducted with infant viral bronchiolitis, WH% also decreased 10  
3 minutes after the administration of epinephrine (ES=-1.09); however it increased in the group of  
4 children administered with albuterol (ES=1.27)<sup>30</sup>. Nevertheless, no significant differences were  
5 found between or within groups. When exploring monophonic and polyphonic WH% significant  
6 change was also not found however, low effect sizes in non-stable and healthy subjects and  
7 medium effect sizes in subjects with stable asthma (ES=-0.54) were found<sup>25</sup>. A significant  
8 decrease in inspiratory and expiratory WH% was found after 3 weeks of pharmacotherapy plus  
9 respiratory physical therapy (ES=-0.66 (inspiratory); ES=-0.64 (expiratory)) or pharmacotherapy  
10 alone (ES=-0.69 (inspiratory); ES=-0.62 (expiratory))<sup>29</sup>. A similar result was found for the  
11 nocturnal WH index, calculated from the WH% (after 2 days (ES=-0.61) and after 6 weeks  
12 (ES=-0.80)), when monitoring respiratory sounds overnight to assess the effects of montelukast  
13 in nocturnal asthma<sup>23</sup>.

#### 14 *Duration*

15 Two studies explored this variable when assessing the impacts of pharmacotherapy with adult  
16 subjects<sup>26, 28</sup>. In both studies WH duration remained approximately the same pre/post  
17 intervention. Only in subjects with moderate and severe obstruction, changes in the duration of  
18 WHs after medication were observed<sup>26</sup>.

#### 19 **Crackles**

##### 20 *Number*

21 Three studies analyzed the number of CRs before and after intervention and no significant  
22 differences were found. In two studies, this variable remained approximately the same, with  
23 effect sizes ranging from 0.02 to 0.22<sup>5, 27</sup>. In the study of Beck et al., the number of CRs  
24 increased (ES=0.58) with albuterol and decreased with epinephrine (ES=-1.65)<sup>30</sup>.

##### 25 *Frequency*

1 The CR frequency was analyzed only in one study<sup>27</sup>. The peak frequency increased during  
2 inspiration (ES=0.11) and decreased during expiration (ES=-0.47) whereas the upper frequency  
3 at -20-dB level decreased in both inspiration (ES=-0.12) and expiration (ES=-0.35). No  
4 significant differences were found.

#### 5 *Two cycle duration (2CD), Largest deflection width (LDW) and Initial deflection width (IDW)*

6 Two studies analyzed the 2CD variable; Marques et al. did not show any change from pre to  
7 post intervention (ES=0.07)<sup>5</sup> and Piirila showed a non-significant reduction post intervention  
8 both in inspiratory (ES=-0.85) and expiratory (ES=-0.83) phases<sup>27</sup>. In the study of Piirila, both  
9 LDW and IDW of inspiratory (ES=-1.25 and -0.38) and expiratory (ES=-1 and -0.76) CRs were  
10 shorter after the intervention<sup>27</sup>.

#### 11 *Timing*

12 Only Piirila explored timing parameters of the CRs related to inspiratory tidal volume and  
13 inspiratory and expiratory phases. These parameters were significantly different post  
14 intervention (ES from 0.5 to 1.14)

15 Due to the heterogeneity of the outcome measures used across studies, a meta-analysis was  
16 not possible to compute.

### 17 **Discussion**

18 The main finding of this systematic review was that ARS detected and characterized by  
19 computerized respiratory sound analysis show potential to be used as outcome measures in  
20 children and adults, as specific variables of each ARS presented high effect sizes. However, the  
21 most appropriate variable(s) or variables are yet to be explored.

22 Most studies (11/12) explored WH presence and characteristics before/after an intervention.  
23 Wheeze occupation rate seemed to be the most promising parameter to be used as an outcome  
24 measure in children and adults, with medium to high effect sizes varying from 0.62 to 1.9<sup>24, 29</sup>. A  
25 strong association between the proportion of the respiratory cycle occupied by WHs and the  
26 degree of bronchial obstruction has been widely demonstrated<sup>21-23, 35</sup>. This WH parameter, even

1 when identified with standard auscultation, has shown to be sensitive to assess the  
2 effectiveness of respiratory interventions in children<sup>36, 37</sup>. The WH complexity may also be a  
3 variable of interest as the presence of polyphonic WHs indicates a more serious obstruction  
4 than monophonic WHs<sup>25</sup> however, this was only explored in one study (ES from 0.24 to 0.54)<sup>25</sup>.  
5 Wheeze monitoring has been found to provide more information on the changes of airway  
6 obstruction than measurements of pulmonary function<sup>24</sup>, such as the percentage predicted of  
7 FEV<sub>1</sub> in people with asthma<sup>26</sup>. Thus, WHs and their variables seem to be a promising objective  
8 outcome measure for all populations with a special emphasis on non-collaborative populations  
9 such as children, people with dementia and people in the intensive care. However, it should be  
10 noticed that WHs only occur when there is a flow limitation (but flow limitation is not necessarily  
11 accompanied by WHs), that reaches a critical value, called flutter velocity<sup>38</sup>. Thus, when there is  
12 not enough flow to generate WHs, WHs parameters will not be useful despite the presence of  
13 the respiratory problem. The complementary information provided by CRs is therefore, crucial.

14 Crackles are assumed to be caused by the sudden opening of abnormally closed airways<sup>39-42</sup>,  
15 and their parameters provide essential information about the function and structure of the  
16 tracheobronchial tree<sup>41</sup>, e.g., CR recording during mechanical ventilation has been considered a  
17 simple method to monitor lung recruitment-derecruitment<sup>43</sup>. However, CR variables have been  
18 explored as outcome measures in only three studies<sup>5, 27, 30</sup>. From the limited evidence available,  
19 LDW seemed to be the most valuable parameter to be used as an outcome measure due to its  
20 high effect sizes (1 and 1.25)<sup>27</sup>. Hoevers and Loudon (1990) had already found that LDW  
21 seemed to be a better measure than IDW or 2CD when differentiating between coarse and fine  
22 CRs<sup>44</sup>. However, LDW was also the variable less explored among studies. Conflicting  
23 information was found for the number of CRs and 2CD. The number of CRs had low effect sizes  
24 reported in Piirila (0.14 and 0.22)<sup>27</sup> and in Marques et al. (0.02)<sup>5</sup> studies, and medium/high  
25 effect sizes in Beck et al. (0.74 and 1.65)<sup>30</sup>. High (0.83 and 0.85)<sup>27</sup> and low (0.07)<sup>5</sup> effect sizes  
26 were also found for the variable 2CD. The timing of CRs (ES 0.5 to 1.14) also showed to be  
27 sensitive to the clinical course of pneumonia<sup>27</sup> and has been described as a sensitive  
28 parameter to discriminate respiratory diseases<sup>45</sup>. However, similarly to LDW limited research  
29 has been conducted considering this parameter as an outcome measure. At this point in time it  
30 is difficult to provide any recommendations on which CR's variable(s) are more adequate to be

1 used as an outcome measure to monitor respiratory interventions. These limited and conflicting  
2 data may be a result of the different respiratory sound acquisition sensors (which differ in their  
3 acoustic sensitivity to capture CRs waveforms), filtering and analysis methods used across  
4 studies<sup>46, 47</sup>. Since CRs show potential for diagnosis purposes but also as an outcome measure  
5 for respiratory treatments in different clinical/research contexts, these procedures need to be  
6 standardized. This will allow comparisons among different studies and improve the  
7 understanding of CRs' mechanisms and acoustic characteristics.

8 The study of both main types of ARS is essential to gather complementary information about  
9 the tracheobronchial tree. This information may help health professionals to conduct more  
10 accurate diagnosis and enhance their understanding about the respiratory system responses to  
11 treatments. However, only one study analyzed both types of ARS as an outcome measure in a  
12 study conducted with children<sup>30</sup>. Thus, the study of computerized ARS is an exciting area where  
13 much research is needed to develop knowledge for diagnosis and monitoring of patients but  
14 also to be used as a non-invasive, objective and reliable outcome measure for treatments.

15 The level of evidence that can be drawn at this moment in time from this systematic review is  
16 considerably weak due to the 1) small sample sizes; 2) distinct respiratory therapies and doses  
17 implemented and 3) different ARS variables used in the included studies. The large variety of  
18 acquisition methods used is an issue added to the list of difficulties when comparing results  
19 across studies. A BIOMED 1 Concerted Action project entitled CORSA, funded by the European  
20 Community, developed guidelines for research and clinical practice in the field of respiratory  
21 sound acquisition and analysis<sup>4, 9, 48</sup>. The CORSA project group produced guidelines on the  
22 definitions of medical/technical terms used in pulmonary acoustics; environmental conditions;  
23 patient management procedures; acquisition, pre-processing, digitization and analysis of  
24 respiratory sounds; and also about publishing the results of research<sup>4, 9, 48</sup>. These international  
25 guidelines have been available since 2000, however from the 9 studies conducted after this  
26 year, only 3 followed the acquisition procedures recommended by CORSA. Regarding the  
27 analysis methods, algorithms based on Fast Fourier Transformation were the most used, which  
28 is in accordance with the CORSA recommendations. Future research, with improved study  
29 designs, larger samples, both of children and adult populations, and following the CORSA

1 guidelines, should be conducted to explore the ARS response to respiratory therapies. This will  
2 facilitate the comparison of results from different studies, promote research into the  
3 development of standardized respiratory sound acquisition equipment and analysis and finally  
4 enhance the understanding of computerized ARS as well as their use as an outcome measure.

## 5 **Conclusion**

6 Specific variables of each ARS detected and characterized with computerized respiratory sound  
7 analysis showed high effect sizes and thus may have potential to be an objective, reliable and  
8 non-invasive outcome measure for respiratory therapy in children and adults. Further research  
9 exploring the ARS response to different respiratory therapies are needed to enhance the  
10 understanding of computerized ARS and their clinical use not only for the diagnosis purposes  
11 but also for monitoring patients and treatments.

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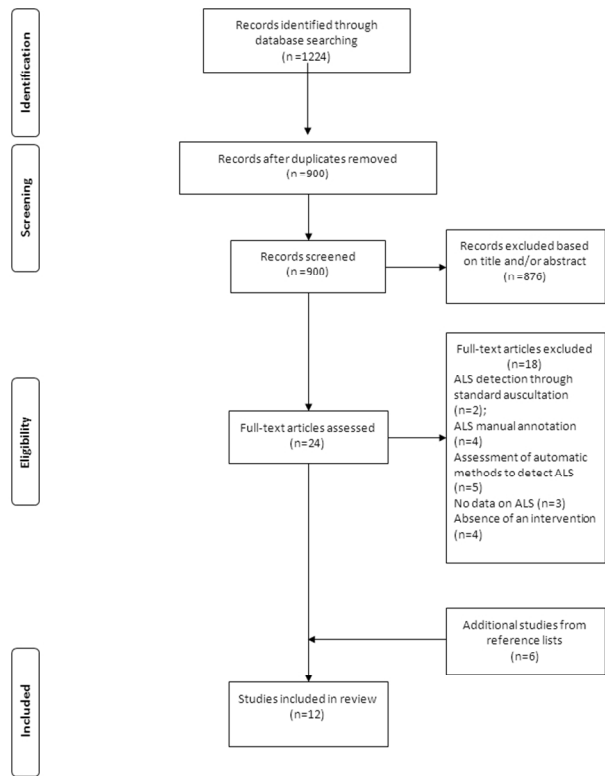
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- 1 Figure captions
- 2 Figure 1 - PRISMA Flowchart of the included studies.

For Peer Review



PRISMA Flowchart of the included studies.  
300x300mm (96 x 96 DPI)



Table 1 - Quality assessment score for selected studies based on the Downs and Black checklist.

Study (year)	Reporting	External validity	Internal validity – bias	Internal validity -	Power	Total Score
	MS=11	MS=3	MS=7	confounding MS=6	MS=1	
Baughman & Loudon (1988)	5	0	6	1	0	12
Piirila (1992)	7	1	3	2	0	13
Sanchez et al. (1993)	6	1	4	0	0	11
Fiz et al. (2002)	7	0	5	0	0	12
Bentur et al. (2003)	8	0	4	1	0	13
Bentur et al. (2004)	8	2	5	2	1	18
Cortes et al. (2005)	6	1	1	2	0	10
Fiz et al. (2006)	8	0	5	3	0	16
Beck et al. (2007)	8	1	7	5	0	21
Marques et al. (2012)	8	1	5	2	0	16
Oliveira et al. (2013)	7	1	4	2	0	14
Dinis et al. (2013)	8	1	5	3	0	17

MS, maximum score.

Table 2 – Characteristics of the adventitious respiratory sounds pre-post intervention.

Study (Year)	Type of study	Participants	Intervention	Data collection protocol	Recording Device	Data Analyses	ALS outcomes	Findings
Baughman & Loudon (1988)	Quasi-Experimental	10 subjects with nocturnal asthma	One night Placebo One night Long-acting $\beta_2$ -sympathomimetic agent – procaterol (0.1mg)	Respiratory sound recordings: - night monitoring of wheezing after intervention at 12am and at 4am; - 6 segments of 5 minutes recordings at each assessment; - microphone of an accelerometer placed over the cricopharynx; - stethoscope over the right anterior chest.	Modified stethoscope air-coupled to a microphone.	<b>WHs</b> detection: FFT Analyses for the presence/ absence of a peak at a frequency 150-1,000Hz.	<b>WH%</b>	<b>Placebo</b> <b>WH%</b> : 12AM 18±5.3%; 4AM 24.8±6.4%; p<0.05 (ES=1.15) <b>Procaterol</b> <b>WH%</b> : 12AM 23.2±6.9%; 4AM 11.8 ±4.0% (ES=-1.9)
Piirila (1992)	Observational	11 subjects with pneumonia 21-71yrs 6M:5F	Standard medical treatment	Respiratory sound recordings: - 2.2±1.1 days after hospital presentation and then after 2.7±1.0 days; - subjects in a sitting position, breathing with a maximum flow of 1L/s; - 5 complete respiratory cycles; - basal regions of both lungs.	Air-coupled condenser microphones	<b>CR</b> detection: <b>Phonopneumograph</b> <b>y</b> FFT <b>TEW</b> Automatic <b>CR</b> counter	<b>CR</b> : N IDW 2CD LDW Beginning Duration End point PF Fu le	<b>Inspiratory CR</b> N: Pre 5±1.9; Post 6± 5.3 (ES=0.22) IDW: Pre 1.5±0.2ms; Post 1.4±0.3ms (ES=-0.38) 2CD: Pre 10.1±1.3ms; Post 8.6±2ms (ES=-0.85) LDW: Pre 2.6±0.4ms; Post 2.1±0.4ms; p<0.05 (ES=-1.25) Beginning: Pre 35±16%Vt; Post 53±19%Vt; p<0.01 (ES=1.02) Duration: Pre 35±13%Ti; Post 36±8%Ti (ES=0.09) End point: Pre 72±13%Vt; Post 83±14%Vt (ES=0.81) le: Pre 69±11%Ti; Post 81±10%Ti; p<0.05 (ES=1.14) PF: Pre 156±46Hz; Post 161±42Hz (ES=0.11) Fu: Pre 437±71Hz; Post 426±106Hz (ES=-0.12)



le: Pre  $0.64 \pm 0.34V$ ; Post  $0.50 \pm 0.23V$  (ES=-0.47)

### Expiratory CR

N: Pre  $0.8 \pm 0.8$ ; Post  $0.7 \pm 0.14$  (ES=-0.14)

IDW: Pre  $1.7 \pm 0.4ms$ ; Post  $1.3 \pm 0.6ms$  (ES=-0.76)

2CD: Pre  $11.9 \pm 2.4ms$ ; Post  $8.1 \pm 5.3ms$  (ES=-0.83)

LDW: Pre  $3 \pm 0.6ms$ ; Post  $2.4 \pm 0.6ms$  (ES=-1)

Beginning: Pre  $56 \pm 14\%Te$ ; Post  $63 \pm 14\%Te$  (ES=0.5)

Duration: Pre  $46 \pm 39\%Te$ ; Post  $22 \pm 0\%Te$  (ES=-0.62)

End point: Pre  $79 \pm 23\%Te$ ; Post  $95 \pm 0\%Te$  (ES=0.7)

PF: Pre  $126 \pm 42Hz$ ; Post  $109 \pm 22Hz$  (ES=-0.47)

Fu: Pre  $365 \pm 127Hz$ ; Post  $327 \pm 69Hz$  (ES=-0.35)

Sanchez et al. (1993)	Quasi-Experimental	EG1: 23 children with cystic fibrosis 4-18yrs 14M:9F CG: 18 healthy children 4-16yrs 7M:11F	Methacholine challenge: doubling concentrations of methacholine nebulized for 2 min (start 0.03mg/ml)	Respiratory sound recordings: - 1min after each dose; - spontaneous breathing; - sounds at trachea and posterior right lower lobe recorded simultaneously.	Piezoelectric accelerometers	WHs detection: FFT Based on PF (auditory verification on digital-to-analog playback)	Presence of WHs	WH as an indicator of bronchial hyperreactivity: Se:50% Sp:100%
Fiz et al. (2002)	Quasi-Experimental	EG1: 16 subjects with asthma 53.6±16.3yrs 9M:7F	Inhalation of terbutaline (1mg)	Respiratory sound recordings: - acquired before and 20min after the intervention; - FVC maneuvers; - at the trachea.	Contact microphone	WHs detection: FFT Modified version of the Shabtai-Musih et al. algorithm	WH frequency	EG1 F: Pre $560.9 \pm 140.8Hz$ ; Post $538.4 \pm 160.5Hz$ ; $p < 0.01$ (ES=-0.15) EG2 F: Pre $669.4 \pm 250.1Hz$ ; Post $620.6 \pm 208.9Hz$ ; $p < 0.01$

		EG2:6						(ES=-0.21)
		subjects with						<b>CG</b>
		COPD						<b>F:</b> Pre 750.7±175.7; Post 701.6±170.1; p<0.01 (ES=-
		58.8±4.9yrs						0.28)
		6M:0F						
		CG: 15						
		healthy						
		subjects						
		45.8±12.5yrs						
		7M:8F						
Bentur et al. (2003)	Quasi-Experimental	12 children with asthma 6-14yrs 6M:6F	Montelukast daily (5mg)	Respiratory sound recordings: - overnight (8h) monitoring of wheezing before the intervention (Pre), after 48 hours (Post 1) and after 6 weeks (Post2); - at the trachea, right and left axillae and both posterior bases of the lungs.	Phonopneumogra phy piezoelectric contact sensors connected to an automatic <b>WH</b> detection device	<b>WHs</b> detection: FFT based algorithm	NWI	NWI: Pre 814±898; Post1 318±199; p=0.05 (ES=-0.61) Post2 137±101; p=0.028 (ES=-0.80)
Bentur et al. (2004)	Quasi-Experimental	28 children with prolonged cough 8.3±4.3mont hs 19M:9F	Acoustic Brochial Provocation tests: Nebulized adenosine solutions (start 0.39 mg/ml) inhaled for 2 min; dose doubled at 5min intervals	Respiratory sound recordings: - after each 2 min of inhalation; - records of 30s; - at the trachea, the axilla right, and the axilla left, and both posterior bases of the lungs.	Phonopneumogra phy piezoelectric contact sensors connected to an automatic <b>WH</b> detection device	<b>WHs</b> detection: FFT based algorithm (an auditory audit of the data was performed to verify the detection accuracy)	Presence of <b>WHs</b>	Presence of <b>WHs</b> : -at 15.6±25.2(0.78-100)mg/mL of adenosine concentration - at an adenosine concentration ≤25mg/mL in 85% of the subjects with positive BPT
Cortes et al.	Observational	G1:10 subjects with	Bronchodilator inhalation drug	Respiratory sound recordings: - acquired before and after 20 minutes of	Phonopneumogra phy piezoelectric	<b>WHs</b> detection: Frequency analysis	<b>WH</b> <b>duration</b>	<b>G1</b> Inspiration: Post <b>duration</b> similar to Pre <b>duration</b>

(2005)	asthma (FEV1<50%) 42±17yrs G2: 11 subjects with asthma (50%<FEV1<80%) 42.2±9.7yrs G3: 5 subjects with asthma (FEV1>80%) 29.2±8.7yrs	the intervention; - spontaneous breathing; - 2 records of 120s; - at the trachea.	sensor	Expiration: Post duration similar to Pre duration <b>G2</b> Inspiration: Post duration < Pre duration Expiration: Post duration < Pre duration <b>G3</b> Inspiration: Post duration similar to Pre duration Expiration: Post duration > Pre duration	
Fiz et al. (2006)	Quasi- Experimental G1: 11 subjects with non-stable asthma 54±15.7yrs 8M:3F G2: 9 subjects with stable asthma 46±12.6yrs 6M:3F CG3: 14 healthy	Bronchodilator inhalation drug (terbutaline - 1mg) the intervention; - FVC maneuvers; - at the trachea.	Respiratory sound recordings: - acquired before and after 20 minutes of the intervention; - FVC maneuvers; - at the trachea.	Phonopneumogra phy contact microphone WHS detection: modification of the algorithm proposed by Shabtai-Musih et al. and Homs- Corbera et al.	<b>WH</b> <b>N</b> <b>F</b> <b>WH%</b> monophoni c <b>WH%</b> polyphonic <b>G1</b> <b>N</b> : Pre 13.6±13.3; Post 13.4±19.6 (ES=-0.01) <b>F</b> : Pre 542.7±185.3Hz; Post 527±62Hz (ES=-0.1) <b>WH%</b> monophonic: Pre 52.5±21.6%; Post 47.7±19% (ES=-0.24) <b>WH%</b> polyphonic: Pre 38.2±25.4%; Post 29.9±23.5% (ES=-0.34) <b>G2</b> <b>N</b> : Pre 3.5±3; Post 5.5±6.8 (ES=0.34) <b>F</b> : Pre 582.2±226.9Hz; Post 583.3±216.5Hz (ES=0.01) <b>WH%</b> monophonic: Pre 27.0±13.4%; Post 19.4±14.9% (ES=-0.54) <b>WH%</b> polyphonic: Pre 16±21.4%; Post 25.2±30.1%

subjects (ES=0.34)

45.4±12.9yrs **G3**

8M:6F **N:** Pre 2.5±2.1; Post 2.3±1.8 (ES=-0.1)

**F:** Pre 732.6±172.2Hz; Post 701.6±170.1Hz (ES=-0.18)

**WH%** monophonic: Pre 37.1±28.7%; Post 48.2±31.6% (ES=0.37)

**WH%** polyphonic: Pre 15.2±18.9%; Post 10.4±10.9% (ES=-0.29)

Beck et al. (2007)	Experimental	G1: 12 children with <b>infant viral bronchiolitis</b> 4.9±0.8mont hs 4M:8F G2: 15 children with <b>infant viral bronchiolitis</b> 4±1.35month s 4M:11F	G1: Nebulized epinephrine (1mg diluted with 2ml of 0.9% saline) G2: Nebulized albuterol (2.5mg diluted with 2.5ml of 0.9% saline)	Respiratory sound recordings: -performed 5min prior to (pre), 10min and 30min post treatment (post1 and post2); - spontaneous breathing; - 5 complete respiratory cycles; - at the right and left axillae and posterior bases of the lungs.	Phonopneumogra phy piezoelectric contact sensors connected to an automatic <b>WH</b> detection device	<b>WHs</b> detection: FFT based algorithm <b>CRs</b> detection: <b>CR</b> counter algorithm (to verify accuracy, segments underwent manual auditory analysis)	<b>WH%</b> <b>CR nBC</b>	<b>G1</b> <b>WH%:</b> Pre 9.1±3.4%; Post1 5.47±3.26% (ES=-1.09); Post2 7.1±3.63% (ES=-0.57) <b>CR nBC:</b> Pre 1.88±0.59; Post1 2.48±0.92 (ES=0.74); Post2 2.26±0.7 (ES=0.58) <b>G2</b> <b>WH%:</b> Pre 5.5±3.08%; Post1 9.11±2.52% (ES=1.27); Post2 11.9±4.5% (ES=1.61) <b>CR nBC:</b> Pre 1.74±0.42; Post1 1.14±0.23 (ES=-1.65); Post2 1.31±0.33 (ES=-1.12)
Marques et	Quasi-	23 subjects	Single physical	Respiratory sounds recordings:	Electronic	<b>CRs</b> detection:	<b>CRs:</b>	nBC: Pre 4.14±2.31; Post 4.18±2.25 (ES=0.02)

al. (2012)	Experimental	with bronchiectasi s 25-73yrs 9M:14F	therapy treatment with ACBT	-before and after the treatment; - spontaneous breathing; - 3 recordings of 25s over each chest location - following the CORSA guidelines for short-term acquisition.	stethoscope connected to a laptop	Vannuccini et al. algorithm BC detection: analogous method to that by Que et al. plus manual adjustment of the detection thresholds	nBC 2CD	2CD: Pre 11.8±1.5ms; Post 11.9±1.54ms (ES=0.07)
Oliveira et al. (2013)	Observational	6 subjects with LRTI 33-63yrs 3M:3F	Standard medical treatment (antibiotics)	Respiratory sounds recordings: -within 24 hours of hospital presentation and after treatment; - spontaneous breathing; -3 recordings of 25s over each chest location -following the CORSA guidelines for short- term acquisition.	Electronic stethoscope connected to a laptop	WHs detection: Taplidou and Hadjileontiadis algorithm based on Short-time FFT	WHs: N F Duration	N: Pre 6±0.9; Post 14.8±2.3; p=0.03 (ES=4.38) F: Pre 365±37Hz; Post 363±29.1Hz (ES=-0.06) Duration: Pre 0.21±0s; Post 0.22±0s (ES=0.11)
Dinis et al. (2013)	Experimental	CG: 11 subjects with LTRI 52.9±18.3yrs 4M:7F EG: 9 subjects with LTRI 49.9±23.2yrs	CG: Standard medical treatment (antibiotics) EG: Standard medical treatment + Respiratory physical therapy (3*week; ACBT, breathing	Respiratory sounds recordings: - within 24 hours of hospital presentation and after treatment; - spontaneous breathing; -3 recordings of 20s; -following the CORSA guidelines for short- term acquisition.	Modified analogue stethoscopes connected to a laptop	WHs detection: Taplidou and Hadjileontiadis algorithm based on Short-time FFT BC detection: Huq and Moussavi automatic	WHs: WH% F	CG Inspiration WH%: Pre 11.1±14.8%; Post 2.2±6.2%; p<0.001 (ES=- 0.69) F: Pre 241.3±60.1Hz; Post 415.5±201.1Hz; p=0.195 (ES=0.97) Expiration WH%: Pre 11.3±13.2%; Post 4.1±7.7%; p<0.001 (ES=-

6M:3F	retraining; incentive	respiratory phase	0.62)
	spirometry; thoracic	detector	F: Pre 221.2±85.6Hz; Post 396.8±208.1; p=0.243
	mobility, expansion	using tracheal	(ES=0.97)
	and flexibility	sounds	<b>EG</b>
	exercises; aerobic		Inspiration
	training)		WH%: Pre 9.2±14.1%; Post 0.4±1.9%; p<0.001 (ES=-0.66)
			F: Pre 360.3±221.1Hz; Post 140.2±153.1Hz; p=0.555 (ES=0.73)
			Expiration
			WH%: Pre 10.5±15.3%; Post 1.9±5.4%; p<0.001 (ES=-0.64)
			F: Pre 423.2±168.6Hz; Post 432.8±269.1Hz; p=0.915 (ES=0.04)
		<b>Post CG vs Post EG</b>	
		Inspiration	
		WH%: 2.2±6.2%; 0.4±1.9%; p=0.019 (ES=0.37)	
		Expiration	
		WH%: 4.1±7.7%; 1.9±5.4%; p=0.061 (ES=0.33)	

For Peer Review

Data are presented as mean±standard deviation

2CD - two cycle duration; ACBT – active cycle of breathing techniques; BC – breathing cycle; BPT – bronchial provocation test; CG – control group; CORSA - computerized respiratory sound analysis; CR – crackle; EG – experimental group; ES – effect size; FFT – fast fourier transformation analysis; F- frequency; Fu - upper frequency at - 20-dB level; FVC- forced vital capacity; IDW - initial deflection width ; Ie - effective intensity; N – number; nBC – number per breathing cycle; NWI - nocturnal wheeze index; PF – peak frequency; Se – sensitivity; Sp – specificity; TEW - time-expanded waveform; WH - wheeze; WH% - wheeze occupation rate.