Conservative management of occult pneumothorax in mechanically ventilated patients

Dr. Jeremy Smith

Master of Clinical Science

JBI

Faculty of Health and Medical Sciences

The University of Adelaide

Australia

December 2020

Contents

Figures

Tables

Abbreviations List

A-a	Alveolar to arterial partial pressure of oxygen difference
ANZCA	Australian and New Zealand College of Anaesthetists
ANZCTR	Australian and New Zealand Clinical Trials Registry
ARDS	Acute respiratory distress syndrome
ATLS	Advanced Trauma Life Support
BPS	Behavioural pain scale
BTS	British Thoracic Society
CI	Confidence interval
COMET	Core Outcome Measures in Effectiveness Trials
CONSORT	Consolidated Standards of Reporting Trials
COPD	Chronic obstructive pulmonary disease
CPOT	Critical-Care Pain Observation Tool
CT	Computed tomography
CVP	Central venous pressure
eFAST	extended Focused Assessment with Sonography for Trauma
ETM	Emergency trauma management
FRC	Functional residual capacity
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICC	Intercostal catheter
ICTR	International Clinical Trials Registry
ICU	Intensive care unit
ISS	Injury Severity Score
IV	Intravenous
JBI	Joanna Briggs Institute
LoS	Length of stay
M-H	Mantel-Haenszel
MAP	Mean arterial pressure
Mx	Management
PAD	Pulmonary artery diastolic pressure
PaO_2	Partial pressure of oxygen
PCWP	Pulmonary capillary wedge pressure
PEA	Pulseless electrical activity
POR	Peto odds ratio
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PTX	Pneumothorax
RCT	Randomised controlled trial
TLC	Total lung capacity
V/Q	Ventilation/perfusion
VAP	Ventilator associated pneumonia
VC	Vital capacity

Abstract

An occult pneumothorax is defined as air within the pleural cavity diagnosed with a computed tomography (CT) scan which has not been suspected on the basis of clinical findings or chest X-ray. The best management strategy has remained unclear, with inconsistencies in the guidelines, literature and speciality opinion. As a high percentage of trauma patients require mechanical ventilation either for general anaesthesia or intensive care stay due to the nature of their injuries, the question of how to manage occult pneumothoraces in this population continues to be raised. The aim of the research presented in this thesis was to investigate the safety and effectiveness of conservative management versus intercostal catheter (ICC) insertion for the management of occult pneumothoraces in mechanically ventilated patients. JBI systematic review methodology and methods were employed to address this aim.

A search for published and unpublished literature included PubMed, Embase, CINAHL, Web of Science, Cochrane Central Register of Controlled Trials, ICTR, ANZCTR and ClinicalTrials.gov. Following the database search, hand searching of reference lists from included articles was conducted. Studies were included if they explored the effectiveness of conservative management versus ICC insertion for the management of occult pneumothoraces in mechanically ventilated patients. Randomised controlled trials (RCTs) and cohort studies were included. Eligible studies were critically appraised by two reviewers using appropriate JBI tools to assess methodological quality. Where required, contact was attempted with corresponding authors for clarifications and further data. RCTs and cohort studies, where appropriate, were analysed in separate meta-analyses using mixed-methods logistic regression. Sensitivity analyses were performed using Mantel-Haenszel and Peto models.

The search yielded 2230 unique citations. Following screening of titles and abstracts, 20 articles were retrieved for full-text screening. Of these, one trial was ongoing and could not be included. Two additional studies were identified through hand searching. Twenty-one full-text articles were screened; eight were ineligible.

Two articles were from the same study, leaving 12 included studies (three RCTs and nine cohort studies) involving 311 participants (135 in RCTs and 176 in cohort studies). One RCT had high methodological quality, while aspects of the remaining two trials were unclear. Overall, the cohort studies fulfilled the majority of the quality appraisal criteria.

For the primary outcomes, analysis of RCTs revealed with conservative management versus ICC insertion: progression of pneumothorax OR 2.36 (95% CI 0.81-6.8, 3 RCTs), ICC insertion (any reason) OR 4.2 (95% CI 0.33-52.5, 2 RCTs). No result was statistically significant. Similarly, considering the remaining outcomes, there were no statistically significant differences, except for ICC insertion (progression to simple pneumothorax); OR 4.8 (95% CI 1.01-23.6, 3 RCTs). Observational data confirmed these trends in the majority of outcomes; however, contradictory results were seen in the outcomes of pneumonia/empyema and ICC insertion (non-pneumothorax reasons). Adverse events included tension pneumothorax and ICC complications. Incidence of tension pneumothorax was 2.5% in the conservative management group and 0.7% in the ICC group. The incidence of ICC complications in the ICC group was 20% versus 3.8% of patients requiring an ICC with conservative management. ICC complications were significantly lower in the conservative management group when an ICC was required in the RCTs (OR 0.12, 95% CI 0.01 – 2.26).

In conclusion, conservative management and ICC insertion appeared equally effective for the management of occult pneumothorax in mechanically ventilated patients. Conservative management can be seen as a safe alternative to ICC insertion, with a low percentage of failure of conservative management reported, a low tension pneumothorax rate and a lower ICC complication rate when an ICC is subsequently required.

Declaration

I, Dr. Jeremy Smith, certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name, in any university or other tertiary institution, and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name, for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide, and, where applicable, any partner institution responsible for the joint-award of this degree.

I acknowledge that copyright of published works contained within this thesis resides with the copyright holder(s) of those works.

I also give permission for the digital version of my thesis to be made available on the web, via the University's digital research repository, the Library Search and also through web search engines, unless permission has been granted by the University to restrict access for a period of time

I acknowledge the support I have received for my research through the provision of an Australian Government Research Training Program Scholarship.

Dr Jeremy Smith

16th October 2020

Acknowledgements

This thesis would not have been brought to completion without the support of a select group of people whom I would now like to acknowledge and thank.

I would first like to thank my primary supervisor, Associate Professor Edoardo Aromataris, for his dedicated approach to ensuring that my best work has been produced in this thesis. He has accomplished this through sharing his vast knowledge and expertise, and taking time out of his busy schedule to keep me on track and provide excellent feedback and explanation when required. Also, I acknowledge my external supervisor, Dr. Paul Secombe, for his support and clinical guidance throughout this process, and the encouragement to pursue this research topic and thesis. It has been a pleasure working with both of you on this research project.

I would also like to acknowledge the guidance on the statistical analysis decision making received from the following statisticians: Professor Jo Leonardi Bee from the University of Nottingham (UK), as well as Jennie Louise and Kelly Hall from the University of Adelaide. Special mention goes to Kelly Hall for assisting in the completion and my understanding of the statistical analysis.

My thanks also go to JBI academic and support staff for instilling the knowledge that was required to complete this thesis through the course work and webinars; the University of Adelaide research librarians, Vicki Langton and Robert Franchini, for their expert assistance with the search strategy; and to Siew Siang Tay who undertook professional copyediting of the thesis in accordance with the Australia Standards for Editing Practice (specifically sections D and E) in a timely manner.

Lastly, acknowledgment goes to my fellow JBI student, Ashish Vaska, for his assistance with the secondary critical appraisal of the included studies.

Chapter 1: Introduction

A previous 'mini-review' on the topic of conservative management of occult pneumothorax was published in 2010[1], including three randomised controlled trials (RCTs), with variable results for and against conservative management. A further review on blunt chest trauma in 2015[2] briefly mentioned management of occult pneumothorax. This review included two RCTs and two retrospective cohort studies that showed no difference in conservative management and intercostal catheter (ICC) insertion for occult pneumothorax.[2] However, there was no explanation as to why one RCT from the earlier review had not been included. Neither of these reviews looked specifically at mechanically ventilated patients or provided a combined estimate of effect. Further published research exists on this topic.

These reviews highlight the inconsistencies within the research of how best to manage occult pneumothoraces, and these inconsistencies are similarly apparent in clinical guidelines. Workplace experience has further highlighted the lack of clear, consistent guidelines, with inconsistent practice seen in the management of occult traumatic pneumothoraces in mechanically ventilated patients and no clear rationale for the choice of management from one patient to another. This lack of consistent clinical practice can potentially lead to adverse outcomes for patients and potentially unnecessary interventions.

The aim of the research presented in this thesis was to clarify the current available evidence so as to ideally and ultimately lead to clearer guidelines addressing the appropriate management of occult pneumothoraces, specifically, in mechanically ventilated patients.

This first chapter of this thesis introduces important topics and issues to facilitate understanding of the research and results presented in this thesis. This includes an introduction to basic lung anatomy, an introduction to pneumothorax (how it occurs, how it is diagnosed and managed, and its life-threatening sequalae, with emphasis on occult pneumothorax), an explanation of the techniques and complications of the common management strategy (ICC insertion), and an introduction to mechanical ventilation and how it affects lung physiology and the pathophysiology of pneumothoraces.

1.1 Lung anatomy

The lungs are half-cone shaped organs that sit within the rib cage, separated by the mediastinum. Anatomically, they include a base (positioned on the diaphragm), an apex (which projects above the first rib into the root of the neck) and two surfaces (see Figure 1.1). The costal surface lies adjacent to the ribs and chest wall, and the mediastinal surface lies against the mediastinum. The right lung is made up of three lobes (superior, middle and inferior) and the left lung has two lobes (superior and inferior).[3]

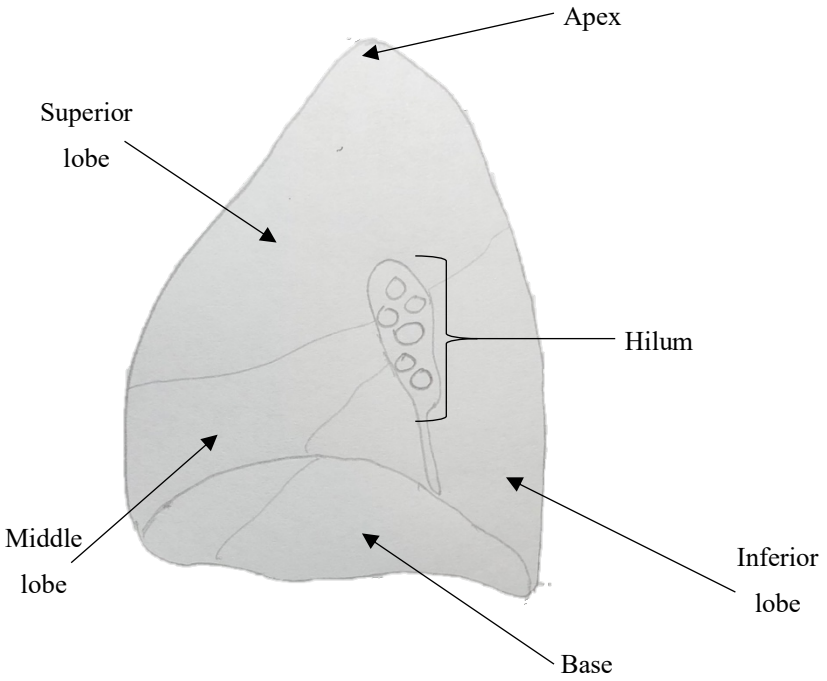


Figure 1.1: Anatomical features of the right lung

Surrounding the lungs is the pleural cavity, a potential space containing a thin layer of serous fluid. It is enclosed by the pleura, which is divided into the visceral pleura (which covers the lungs) and the parietal pleura (which covers the chest wall, diaphragm and mediastinum) (see Figure 1.2). These two divisions attach at the hilum of the lung, at which blood vessels, bronchi and other structures enter the lung[3] (see Figure 1.1). The pressure in the pleural cavity is usually negative relative to atmospheric pressure due to the outward force of the rib cage and the tendency of the lung to collapse, creating opposing elastic forces.[4]

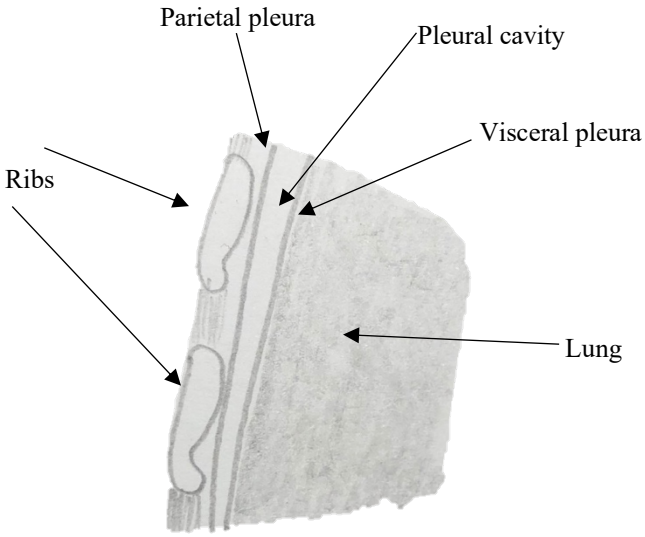


Figure 1.2: Pleural cavity

1.2 Pneumothorax and occult pneumothorax

A pneumothorax, commonly referred to as a 'collapsed lung', is the pathological presence of air within the pleural cavity.[5,6] It occurs due to the development of a connection between the lung and pleural cavity, or between the atmosphere and pleural cavity through the chest wall.[7] This connection allows air to move into the pleural cavity down a pressure gradient (see Section 1.2.1).

An occult pneumothorax is defined as air within the pleural cavity that is diagnosed with a computed tomography (CT) scan but which has not been suspected on the basis of preceding clinical examination or chest X-ray.[8-10] Occult pneumothorax was first described in the literature by Wall et al.[11] in 1983 after the authors diagnosed pneumothoraces following abdominal CT scans that had not been diagnosed with preceding chest X-ray. It was further described by Tocino et al.[12] a year later, after pneumothoraces were identified at lung apices from CT scans of the head. Extended focused assessment with sonography for trauma (eFAST) is commonly used in trauma, and as such ultrasound has been used as another method to diagnose occult pneumothoraces[13], however, CT scan remains the gold standard.[13,14] The overall incidence of occult pneumothorax in trauma patients is reported to be around 5%[8,9], however not all trauma patients receive a CT scan so the incidence is likely to be higher. Trauma patients who are severely injured will

receive a CT scan; in this scenario the incidence of occult pneumothorax has been reported to be as high as 56%.[15,16] CT scans have become more common place following traumatic injuries, with a study showing increased use of CT scans for blunt trauma over the period 1998-2004, increasing from 2.7% to 28.7%.[17] This is likely due to CT scanners becoming increasingly more sensitive, with higher resolution and thinner slices.[18,19] They have also become much faster and use less radiation[18,19], which makes it a safer procedure for the patient. Due to the increased utilisation of CT scans in trauma patients, more occult pneumothoraces will be diagnosed.

1.2.1 Pathophysiology

Pneumothorax occurs because the pressure in the pleural space is always less than both the alveolar and atmospheric pressure. Therefore, if any connection occurs through the parietal or visceral pleura, air will flow into the pleural space until the pressure is equalised or the connection is closed.[6,20]

Pneumothoraces have respiratory and cardiovascular effects, the full extent of which is not completely known. There are a limited number of studies in this area, most of which have been on animal models. The known effects to the respiratory system include decreased lung volumes and reduced PaO_2 (arterial partial pressure of oxygen).[6] Gilmartin et al.[21] measured spirometry in six patients with pneumothoraces and showed that there was a decrease in vital capacity (VC), functional residual capacity (FRC) and total lung capacity (TLC), and that the pneumothorax produced a restrictive ventilatory defect. These decreased lung volumes are often well tolerated in healthy individuals, especially in smaller pneumothoraces. Results of a study by Kilburn[22] using a dog model suggest this is likely due to compensatory mechanisms, including decreased dead space and an increase in the respiratory rate to maintain a normal minute volume. Considering there are a few possible mechanisms for decreased PaO_2, the answer is likely multifactorial. However, the main suspected mechanism is anatomical shunts. This is supported by a study on humans by Norris et al.[23]; the authors showed that after a pneumothorax has reduced lung volume by 25%, there is a near linear correlation between an increasing shunt (area of the lung which has blood flow but no ventilation) and decreased lung volume. The authors also suggested that the

increased A-a gradient (difference between the alveolar and arterial partial pressure of oxygen) could be completely explained by the shunt.[23] Shunts causing the decreased oxygenation is supported by Moran et al.[24] who showed, again on a dog model, that the relative blood flow of the ipsilateral lung to the pneumothorax was not altered, however there was a reduction in ventilation, due to the closure of small airways as the lung volume decreased.[25] This led to a decreased ventilation/perfusion (V/Q) ratio in the ipsilateral lung.

A small to moderate pneumothorax has limited effect on the cardiovascular system[6]; the effects of a larger pneumothorax will be described in the next section.

1.2.2 Tension pneumothorax

Tension pneumothorax is a life-threatening condition. It is thought to occur due to the presence of a one-way valve phenomenon in the connection through the pleura.[26] Mechanical ventilation is thought to increase the risk of progression to tension pneumothorax due to positive pressure in the lung, promoting movement of air into the pleural cavity.[6] Tension pneumothorax can be defined using intrapleural pressure, clinically or radiologically. In terms of intrapleural pressure, tension pneumothorax occurs when intrapleural pressure exceeds atmospheric pressure throughout expiration and often during inspiration.[6] Clinically, it can be defined as haemodynamic compromise with improvement following release of gas on insertion of an ICC, or a hiss of air on thoracic needle decompression.[26] It can also be defined by features on a chest X-ray, which can include mediastinal shift, depression of ipsilateral diaphragm, and a pneumothorax occupying greater than 50% of the hemithorax volume.[27] However, a tension pneumothorax should be treated prior to imaging of the chest, if suspected.

The physiological effects of a tension pneumothorax depend on whether the patient is mechanically ventilated or spontaneously breathing unassisted[26] and also on the mode of ventilation (i.e. pressure or volume control).[28] Studies in spontaneously breathing animals have shown progressive hypoxaemia, with maintenance of cardiac output.[29] In these studies, the progressive hypoxaemia was likely due to shunts, suggested by maintenance of minute volume and normocapnia, and cardiac output was maintained despite a decreased stroke volume through compensatory tachycardia.[26] Decompensation occurs due to severe hypoxia causing sudden

cardiovascular collapse. The proposed pathophysiology of tension pneumothorax in unassisted spontaneously breathing patients is lung collapse, leading to shunts and hypoxaemia. The lack of cardiovascular effects in this group of patients is thought to be due to increased ability to mount a tachycardic response, incomplete transmission of pressure to mediastinum/major vessels and maintenance of venous return through a siphon effect from increased negative contralateral intrathoracic pressures.[27]

Studies in ventilated animals and patients have shown that cardiovascular effects predominate. Multiple studies[28,30-32] in ventilated animals have shown a significant decrease in cardiac output and mean arterial pressure (MAP) as the pneumothorax increases in size. This decrease in cardiac output and MAP will eventually lead to PEA (pulseless electrical activity) cardiac arrest[27,28] (defined as a cardiac arrest where there is loss of cardiac output despite ongoing electrical activity of the heart). In these studies, this occurred with maintenance of oxygen saturation. A case series in patients with tension pneumothoraces supported the decreased cardiac output and MAP, and revealed a mild decrease in oxygenation.[33] The haemodynamic effects are consistent in the literature, however there are some inconsistencies in the effect on oxygenation.[26] The suggested pathophysiology in ventilated patients is impaired compensatory mechanisms (i.e. tachycardia) due to sedation and increased airway pressure obstructing venous return and blood flow through the lung (via increased pulmonary vascular resistance).[26,27]

An interesting study by Nelson et al.[28] explored the differences in the cardiorespiratory response to tension pneumothorax in volume and pressure controlled ventilation on a pig model. The authors found that in volume controlled ventilation (a ventilation mode where the tidal volume is set for each breath), as they increased the pleural pressure there was a decrease in the cardiac output and MAP.[28] There was also a slower rise in central venous pressure (CVP) and pulmonary artery diastolic pressure (PAD)/ pulmonary capillary wedge pressure (PCWP), and a sharp decline in cardiac output and MAP, when there was equalisation of CVP and PAD/PCWP.[28] This rapid decline led to PEA cardiac arrest, which was reversible with decompression of the tension pneumothorax. There was no desaturation during this time, as ventilation was maintained by increasing airway pressures. In pressure controlled ventilation (a ventilation mode where the pressure applied to the lungs is

set for each breath), they found that there was a rapid decrease in tidal volume as the pleural pressure increased. This led to a rapid decrease in oxygen saturation and eventual bradycardia, hypotension and asystolic cardiac arrest secondary to the hypoxaemia.[28]

Due to the life-threatening nature of tension pneumothoraces, immediate recognition and treatment are important. Recommended treatment is immediate needle decompression or finger thoracotomy, followed by insertion of an ICC.[34,35]

1.2.3 Signs and symptoms

Common symptoms of a pneumothorax include chest pain and dyspnoea (shortness of breath). Chest pain is commonly described as 'sharp' in nature and localised to one side of the chest.[6] The signs of a pneumothorax are dependent on its size, with a small pneumothorax often being asymptomatic.

Signs include expansion of the chest on the affected side with decreased movement during the respiratory cycle, absent or reduced breath sounds, hyperresonance to percussion, loss of tactile fremitus (palpation of chest wall to detect changes in vibrations during speech) and subcutaneous emphysema (air within subcutaneous tissue that can be felt during palpation).[6,36,37] Rare signs include shifting of the liver inferiorly with right sided pneumothorax[6] and clicks which are synchronised with the cardiac cycle with left sided pneumothorax (Hamman's sign).[36]

Late signs, which may suggest progression to tension pneumothorax (see Section 1.2.2), include tachycardia, hypotension, cyanosis and deviation of the trachea away from the side of the pneumothorax.

1.2.4 Pneumothorax categories

Pneumothoraces can be categorised as spontaneous, iatrogenic or traumatic, based on their cause.

1.2.4.1 Spontaneous pneumothorax

Spontaneous pneumothorax occurs without a clear cause. It can be divided into primary and secondary. Primary spontaneous pneumothoraces occur in otherwise healthy individuals, commonly in their early twenties. The mechanism of this is not completely understood.[6] Secondary spontaneous pneumothoraces occur in

individuals with previous lung disease, e.g. chronic obstructive pulmonary disease (COPD), connective tissue disorders, asthma, lung cancer and lung infections.[36]

1.2.4.2 Iatrogenic pneumothorax

Iatrogenic pneumothorax occurs due to a diagnostic or therapeutic intervention (i.e. lung biopsy, intercostal block, ICC insertion, central venous catheter insertion). It can be inadvertent or intended.[6,37] Iatrogenic pneumothorax can also occur via pulmonary barotrauma (see Section 1.5.3) in a patient who is mechanically ventilated. This is more common when high volumes and pressures are used.[38]

1.2.4.3 Traumatic pneumothorax

Traumatic pneumothorax can be caused by penetrating or blunt trauma. In blunt trauma, pneumothorax can occur via three mechanisms. First, fractured or dislocated ribs can lacerate the pleura or lung parenchyma. In the case of no rib fracture/dislocation, which is common, there are two suspected mechanisms: either increased alveolar pressure, which can occur during sudden chest compression, leading to rupture of alveoli; or, uncommonly, increased pressure during the phase where the glottis is closed in the level of the bifurcation of the trachea and/or where bronchi separate, leading to rupture in the larger airways.[7,39]

The mechanism in penetrating trauma is simpler and more direct, with air allowed to enter the pleural space through the chest wall or from the lungs due to damage to the pleura.[7,39]

1.2.5 Diagnosis

Pneumothorax may be suspected following clinical examination based on observation of common signs and symptoms (see Section 1.2.3), however is confirmed (except in the case of a suspected tension pneumothorax, which requires urgent treatment) with one of the following imaging modalities.

1.2.5.1 Chest X-ray

Pneumothorax can be diagnosed with an erect chest X-ray in most cases: by a visceral pleural line seen without distal lung markings.[40] The size of a pneumothorax can be misleading on chest X-rays, with a 2cm margin of gas peripheral to the lung corresponding to 30-50% collapse.[7,40] Small pneumothoraces can be difficult to diagnose with chest X-rays of trauma patients, as imaging often

occurs with the patient in the supine position due to potential spinal injuries. Supine chest X-rays are inaccurate for diagnosing pneumothoraces as they result in air spreading out over the anterior chest.[7,41] The sensitivity of supine chest X-rays is 12-24% and specificity is 89-100%.[42] There are some subtle signs in a supine chest X-ray that can indicate the presence of a pneumothorax, but they are difficult to observe and confirm in the emergency setting due to small screens, bright lights and time pressure. These can include subcutaneous emphysema (air within the subcutaneous tissue seen with chest X-rays which is almost always an indicator of pneumothorax), deep sulcus sign[43] (deepening of lateral costophrenic angle, a common sign), hyperlucent hemithorax and depressed/inverted diaphragm (can be a sign of impending tension pneumothorax).[40,44-46] Rarer signs include the double diaphragm sign[45] (second distinct line overlying the diaphragm, may represent thin line of air above diaphragm), sharpened cardiac silhouette/black stripe sign[44] (thin layer of air extending along mediastinal and cardiac margins) and a floating pericardial fat pad[47] (elevation of cardiac fat pad).

Due to the issues with supine chest X-rays in trauma, there is a concern that some of the pneumothoraces seen on CT scans may be missed on the initial chest X-ray. Two studies[42,48] have retrospectively investigated whether these pneumothoraces, reported as occult, have been actually missed on preceding chest X-rays. They found that less than 20% of the reported occult pneumothoraces were missed and these were found due to inferences from subtle signs such as deep sulcus sign and subcutaneous emphysema.

1.2.5.2 Computed tomography scan

CT scans are not used to diagnose spontaneous pneumothoraces, however, they may be used to determine an underlying cause. In trauma situations, CT scans are often ordered based on the mechanism of accident and injury (e.g. high-speed motor vehicle accident, fall from height), without necessarily any overt signs of underlying injury due to the high risk of occult injuries. CT scans are used to identify spinal injuries, intra-abdominal injuries and occult life-threatening injuries (such as aortic injuries).[35,49] Occult pneumothoraces are often an incidental finding in these trauma CT scans. Due to the ability of CT scans to accurately report sizing and location of a pneumothorax, they are the gold standard for diagnosing traumatic occult pneumothoraces.[13,14]

1.2.5.3 Ultrasound

Lung ultrasound is a relatively new technique (introduced over the last 20-30 years), as it was initially thought that air-filled lungs are not conducive to ultrasound techniques. This is due to air not being able to transmit ultrasound waves, which causes a large amount of artefact.[50,51] A better understanding of these artefacts has led to the increased use of lung ultrasound in the diagnosis of a number of conditions, including pneumothorax.[51,52] The first artefact to be used for the diagnosis of pneumothorax was lung sliding.[50] Lung sliding is the to-and-fro movement (also described as twinkling movement) visible at the pleural line, synchronised with respiration. It corresponds to the visceral pleura sliding in contact with the parietal pleura.[14,53,54]

The absence of lung sliding is highly suggestive of a pneumothorax, with a specificity of 78-100%.[50,52,55] However, there are a number of other conditions that can cause loss of lung sliding. These include inflammatory conditions (i.e. acute respiratory distress syndrome [ARDS]), right main bronchus intubation/one lung ventilation, cardiac arrest, apnoea, lung fibrosis, chronic adherences and phrenic nerve palsy.[53,56] Due to this, other artefacts have been used to help improve the accuracy of lung ultrasound for diagnosis of pneumothorax. A-lines are horizontal repetitions of the pleural line that are caused by reverberation artefacts. In a normal lung, these reverberations will continue for a short period, and in a pneumothorax they continue throughout the image. It can be visualised better in M-mode (images one slice of ultrasound over time), with a seashore sign[53] seen in normal lung and a barcode or stratosphere sign[51] seen in a pneumothorax. B-lines are vertical lines (comet-tail artefacts) that arise from the pleural line, visualisation of B-lines excludes a pneumothorax.[14,57] A lung point is described as an ultrasound window obtained between two ribs, where lung sliding is seen in part of the view and not the other. This is due to the sliding lung intermittently coming into contact with the chest wall during inspiration.[14] Visualisation of the lung point sign is pathognomonic for pneumothorax[53] and can be useful in assessing the size and extent of pneumothorax.[51] In a large pneumothorax, a lung point may not be seen[54] due to no part of the lung coming into contact with the anterior chest wall. The overall sensitivity and specificity of lung ultrasound for pneumothorax vary slightly in the literature, ranging from 60% to 95% and from 90% to 100%,

respectively[14,50,58,59], depending on the study. These variations can likely be explained by differences in patient populations, differences in operator experience[56,57] and the artefacts used.

Ultrasound outperforms chest X-ray for diagnosis of pneumothorax, especially occult pneumothorax.[13] It is not as sensitive or specific as CT scans, however it has the benefit of being a rapid, clinician performed, bedside test.[60]

1.3 Management of occult traumatic pneumothorax

Although occult pneumothorax was first identified over 30 years ago, there is no consensus on the best management strategy; this is especially the case with patients receiving mechanical ventilation. There are no clear guidelines and there are inconsistencies in the literature and medical practice. The two possible approaches are conservative management (or observation) and insertion of an ICC, both of which have their own advantages and disadvantages.

Conservative management involves a combination of serial examination and serial imaging (mostly chest X-rays) to monitor pneumothorax progression. These patients are managed in a highly monitored environment, with high medical and nursing staff to patient ratios. During conservative management, resolution of the pneumothorax occurs due to reabsorption of air from the pleural space. How quickly this occurs depends on the gradients of various gases between the pleura and the venous blood.[4]

Management with an ICC removes air directly from the pleural space into a drain outside the body via the inserted catheter. It is a faster method of removing the air, however it involves an invasive procedure and associated complications (see Section 1.4).

The main source of trauma education internationally is the Advanced Trauma Life Support (ATLS) course. Until recently, it recommended that all patients with pneumothoraces undergoing general anaesthesia or mechanical ventilation require insertion of an ICC.[61] The most recent manual update (edition 10[35]) is less descriptive, stating that ideally a patient with a known pneumothorax should not undergo general anaesthesia or receive mechanical ventilation without having an ICC. However, in selected circumstances (i.e. subclinical/occult pneumothorax), the

trauma team may decide to carefully observe the patient. The guidelines highlight the risk of tension pneumothorax while receiving mechanical ventilation. This is more in keeping with the guidance from the Emergency Trauma Management (ETM) course[34] (a recently formed Australasian critical care focused course). It states that the classical teaching is that an ICC should be inserted if mechanical ventilation is required, however in centres with experienced staff, small/occult pneumothoraces may be closely observed.

Inconsistencies in medical practice are confirmed by a survey completed in the UK, showing disagreement between medical specialties that commonly manage this group of patients, with prophylactic placement of an ICC varying from 28% to 100%.[62] Inconsistencies are also prevalent in the results of studies investigating management of occult pneumothorax. The first RCT on the topic, by Enderson et al.[63] in 1993, reported development of tension pneumothorax in three out of 15 patients, with a further five requiring ICC placement for pneumothorax progression. From this study, it was recommended that all patients with occult pneumothorax who require mechanical ventilation also receive a prophylactic ICC. Studies completed in the last decade have reported one tension pneumothorax with no mortality for conservative management and have reported a 'failure' of conservative management (defined as requirement for ICC insertion) between 8-30%.[10,64,65] Despite this apparent high failure rate, the corollary is that at least 70% of patients had avoided an unnecessary procedure, with its high complication rate and associated pain. There have also been some earlier reviews on this topic[1,2] which have had a small number of trials included (three RCTs in the first, and two RCTs and two cohort studies in the second) and have suggested, with low certainty, that conservative management may be safe.

Due to the theoretical increased risk of tension pneumothorax in patients receiving mechanical ventilation, prophylactic insertion of an ICC is common. Unfortunately, ICC insertion is not without risks and is associated with a major complication rate of approximately 20%.[66] These risks are discussed below (see Section 1.4.3). Placement of an ICC does not completely reduce the risk of tension pneumothorax, due to the risk of malpositioning[67], and may actually delay the diagnosis of a tension pneumothorax due to the assumption that the pneumothorax has been effectively treated.

Due to the lack of consensus in the guidelines and literature, there is a risk of harm to patients due to clinical practice variations.

1.4 Intercostal catheter

Thoracic drainage has been reportedly in use since Hippocrates in approximately 400BC[68]; it has had an interesting development trajectory since then to the modern ICC. This section discusses the different insertion techniques of an ICC, parts of the anatomy important for insertion, how drainage works, and the complications associated with ICC insertion.

1.4.1 Insertion techniques

There are two main insertion techniques for ICCs. The first is the Seldinger technique, which uses a needle, wire and dilator. The other is a surgical technique, which most commonly uses blunt dissection into the thoracic cavity between two ribs. A third, the trocar technique, is now rarely used due to the high complication rate associated with its use.

1.4.1.1 Safe insertion site

The British Thoracic Society (BTS) recommends a safe zone for insertion of an ICC, termed the 'safe triangle'.[69,70] This safe triangle is bordered by the lateral edge of the latissimus dorsi and the lateral border of pectoralis major, and is superior to the horizontal level of the fifth intercostal space. The apex of the triangle is the axilla. Some advocate a 'quadrangle of safety', which has a superior border of the third intercostal space.[71] A study from the UK reported that, of a sample of 50 junior doctors, only 22 doctors' planned insertion sites fell within the safe triangle[72], showing that this safe insertion site is not well understood.

Most guidelines[70,71,73] recommend inserting the drain just superiorly to the inferior rib in the chosen intercostal space due to the classic teaching that the neurovascular bundle sits in the subcostal groove, which is just at the inferior border of the rib. However, this may not be the case. A cadaveric study by Wraight et al.[74] found that there were considerable variations in the position of the neurovascular bundle and suggested a narrow 'safe zone', 50-70% down the chosen intercostal space.

1.4.1.2 Seldinger technique

The Seldinger technique was first described in 1953 as a method for inserting a catheter into an artery for percutaneous angiography.[75] It has since been modified to be used for a number of procedures within critical care, including a technique for small-bore chest drain insertion. This technique is used for catheters 20 French or less and can include straight or flexible pigtail catheters.[76]

The technique involves the following steps[70,71,76,77]:

1. Infiltrate local anaesthetic in insertion site, then use local anaesthetic needle as 'seeker' needle to confirm correct insertion site.
2. Insert larger needle until confirmed in pleural space (by aspirating air or pleural fluid).
3. Insert guidewire through needle so at least half the wire is in pleural cavity.
4. Remove needle, leaving guidewire *in situ*.
5. Pass dilator over guidewire to create a tract.
6. Remove dilator and pass catheter over guidewire.
7. Remove guidewire.
8. Secure catheter and connect to drain.

This technique is less painful than surgical techniques[78] and negates the need for a large incision.

1.4.1.3 Surgical technique – blunt dissection

Surgical techniques are used when larger chest drains (>20 French) are required and are often used in the immediate management of trauma patients for large pneumothoraces or haemothoraces.[73,76]

The technique uses the following steps[70,71,73,76,77,79]:

1. Infiltrate local anaesthetic widely over incision area.
2. Make an approximately 2cm wide incision (large enough for introduction of finger into pleural space) aligned to chosen intercostal space.
3. Use large clamp (artery forceps, Kelly clamp or Harrison-Cripps forceps) to bluntly spread pericostal layers, until parietal pleura is breached.
4. Place finger in pleural space alongside clamp and explore tract with finger, ensuring lung falls away from pleura ('finger sweep'). Once finger is in pleural space, clamp can be removed.

5. Use clamp to help place catheter past finger into pleural space; once catheter is in pleural space, unclamp and advance tube using finger to direct tube in desired direction, ensuring most distal hole is in pleural space.
6. Secure catheter (sutures and dressing), suture skin closed around catheter and connect to drain.

1.4.1.4 Surgical technique – trocar

The trocar technique uses a chest tube that is fitted with an internal sharp and rigid metal obturator, which is used to penetrate the subcutaneous tissues using a twisting motion. The trocar is inserted until a 'pop' sound is heard on entrance into the pleural space.[79] The BTS guidelines recommend that trocars should not be used.[70] This is due to the high complication rate when trocars are used[80], including damage to essential intrathoracic structures and malpositioning. This is further discussed below (see Section 1.4.3).

1.4.2 Drainage

Drainage of a pneumothorax can be done via a Heimlich valve[81,82] (a type of one-way valve) that connects to the end of the catheter, the benefit of which is better portability than larger drainage systems. However, the most common and safest method is an underwater seal drain. Modern underwater seal drains use a three-compartment system. The first is a collection chamber, which allows measurement of fluid drained from the lungs. The second is the underwater seal, which acts as a one-way valve, letting air exit from the pleural space on exhalation and preventing air from entering the pleural cavity on inhalation.[83] The third compartment allows for negative pressure to be applied to the pleural cavity in order to facilitate re-expansion of the lung via the application of suction.[84] These three compartments are combined into one container for easy use and movement.

1.4.3 Intercostal catheter complications

In the literature, the incidence of ICC complications is reported to be around 20-35%.[66,85-89] A recent study from Iran reported a complication rate higher than 60% for ICC insertion performed by surgical and medical residents.[90] ICC complications are reduced when the trocar is not used.[91-93] A South African study[94], where 75% of

insertions used a trocar, reported 58 organ injuries in 53 patients (i.e. some patients had more than one organ injury from their ICC insertion). ICC complications, even tube malpositioning, are clinically important as they increase intensive care unit (ICU) and hospital length of stay.[95]

ICC complications can be subdivided in a number of ways and are reported inconsistently in the literature.[88] In this thesis, they have been divided into the subcategories of insertional, infectious, mechanical, post removal and other.

1.4.3.1 Insertion

The most common complication of ICC insertion is catheter malpositioning.[91] It occurs most commonly with urgent ICC insertion due to suboptimal positioning, with less experienced operators or with pre-existing pulmonary pathology. The types of malpositioning include chest wall placement (tip of catheter in subcutaneous tissue), intrafissural (tip of catheter in lung fissure), intraparenchymal (tip of catheter in lung tissue, more common in the presence of adhesion or pre-existing lung disease), mediastinal placement and abdominal placement.[91] The catheter may also be malpositioned across the anterior mediastinum when using a trocar, which can cause a contralateral pneumothorax.[96] Catheter malpositioning will lead to no or inadequate drainage and may not be appreciated until there is clinical deterioration, as it may be missed with a post insertion chest X-ray. CT scans may be required to fully appreciate the malpositioning, especially with intraparenchymal or intrafissural placement.[97,98]

Damage can occur to any structure within the abdominal and thoracic cavity, including organs, blood and lymph vessels, and nerves. Organ injuries can occur both within the thoracic cavity (lung, heart and oesophagus) and outside the thoracic cavity (liver, spleen, stomach and diaphragm). In the thoracic cavity, the lung is the most commonly injured organ.[99] A laceration of the lung can occur during insertion; this is often more common when inserting an ICC for non-pneumothorax reasons and can lead to a bronchopleural/alveolar-pleural fistula (an ongoing leak of air into the pleural space), which may require surgical repair.[100] Cardiac and oesophageal injuries are rare[99], however perforation of the oesophagus and catastrophic penetrating injury to the heart have been reported. Compression of critical cardiac or vascular structures can also lead to haemodynamic compromise.[101]

The liver and spleen are the more common abdominal organs injured with ICC insertion, due to their close proximity to the diaphragm, however this has become less common with the decreased use of trocars for insertion. Gastric and bowel perforations are rare but have been reported.[99,100] Damage to the diaphragm can also occur, including laceration, perforation and muscle dysfunction.[100]

Damage to blood vessels leads to haemorrhage, which can be serious, and blood loss into the pleural cavity can occur. The most common site of vascular injury is the intercostal arteries[91,100] (see Section 1.4.1.1). Other potential vascular injuries include injury to the pulmonary arteries and occlusion of the subclavian artery.

Nerve injury is rare, however damage can occur to the phrenic nerve, vagus nerve and sympathetic trunk. Phrenic nerve palsy and acute diaphragmatic paralysis can occur (most frequently in neonates) due to compression of the phrenic nerve in the mediastinum.[100] Injury to the sympathetic trunk can occur when an ICC is inserted high into the apex of the pleura[100], and may result in Horner's syndrome (which consists of miosis, ptosis, anhidrosis and enophthalmos). Thoracic duct damage can occur, causing a lymph fluid leak into the pleural space. This is a rare complication that is evident through milky drainage fluid that, when analysed, will show high triglyceride levels.[100]

Insertion of a catheter or insertional wire into the thoracic cavity can cause mechanical stimulation of the heart, pericardium or vagus nerve. This can cause cardiac dysrhythmias, including atrial fibrillation and severe bradycardias.[91]

Even when the catheter is positioned correctly, there is potential for an insertional complication if the lung re-expands too quickly. Re-expansion pulmonary oedema is a rare condition (incidence is around 1%[102]) that can occur on expansion of the lung during drainage of a pneumothorax or pleural effusion. It affects the ipsilateral lung and appears to be due to increased endothelial permeability and loss of integrity of the alveolar capillaries.[91] The clinical picture can vary from asymptomatic chest X-ray changes, to mild respiratory symptoms with pink frothy sputum and tachypnoea, to dramatic respiratory failure. It often self-resolves over a few hours. The risk factors for its development include young age, large pneumothorax (greater than 30% of the hemithorax), pneumothorax for greater than three days and greater than three litres of pleural fluid drained.[91,102]

1.4.3.2 Infection

As with any foreign material that is inserted into the body, there is a risk of infection with an ICC. Infection at the insertion site is the most common and can occur both while ICC is *in situ* and post removal. The incidence of insertion site infection has been reported to be 7.7%.[91] It is diagnosed based on the presence of erythema and swelling of surrounding skin and is treated with intravenous (IV) antibiotics. It often requires the removal of the ICC to eradicate infection.

More serious infectious complications include empyema and necrotising chest wall infections. An empyema is an infected collection of fluid/pus within the pleural cavity. Its incidence is around 1-2%.[66,103,104] Risk factors for developing an empyema include penetrating mechanism, prolonged ICC dwell time, lung contusion, retained haemothorax, need for laparotomy and prolonged ICU stay. The most important of these appears to be retained haemothorax[104,105], due to blood being a good medium for bacterial growth. Empyema often requires a surgical thoracotomy for wash out, along with IV antibiotics. Necrotising chest wall infections are very rare and most commonly occur in the setting of empyema drainage. It is a rapidly progressive life-threatening infection of the subcutaneous tissue that requires urgent surgery for debridement of necrotic tissue and broad-spectrum IV antibiotics.[99,100]

1.4.3.3 Mechanical complications

Mechanical complications are defined as those relating to the catheter itself and include dislodgement, occlusion and erosion into surrounding structures. Dislodgement and occlusion often require placement of a new ICC. Catheter dislodgement is more common in pigtail catheters as they are often not secured as tightly as larger ICCs.[106] Agitated patients may also self-remove ICCs.

Catheter occlusion can occur via blockage or kinking. Both are more common with small bore catheters. Blockage is more common when draining an effusion or haemothorax.[106] The rate of blockage can be decreased by intermittently flushing the catheter.[106] Catheter occlusion can cause accumulation of pneumothorax or haemothorax, which can lead to clinical deterioration.

Erosion into thoracic structures is a very rare delayed complication. Continued direct contact between catheter and structures, along with constant motion due to respiration or cardiac rhythm is the most likely mechanism behind this.[99]

1.4.3.4 Complications post removal of intercostal catheter

Recurrence of the underlying condition is the main concern after removing an ICC. Recurrent pneumothorax following catheter removal can occur due to removing ICCs before the lung has fully expanded, bronchopleural/alveolar-pleural fistula or entrainment of air during removal.[91] Risk factors for recurrence or development of a pneumothorax after catheter removal include younger age, penetrating mechanism and thin chest wall.[107] Recurrent haemothorax/pleural effusion occurs due to ongoing pathology (e.g. bleeding or increased pleural fluid production) or if the ICC cannot drain all the fluid (due to positioning or loculation of fluid). Rare complications post removal of ICCs includes retained catheter fragment (which can occur if damage to the catheter occurs on insertion[100]) and herniation of lung out of previous ICC site (very rare, but case reports exist[91]).

1.4.3.5 Other complications

Recurrent pneumothorax during ICC dwelling can occur if there is not an adequate seal with an occlusive dressing over the ICC insertion site. Pneumothorax re-accumulation occurs via air being entrained into the pleural cavity via the ICC tract. Once the seal is returned, the pneumothorax can again drain through the ICC.[99]

1.4.4 Removal of intercostal catheter

The decision to remove an ICC depends on the indication(s) for its insertion.

If inserted for a pneumothorax, it can be removed when there is no longer evidence of pneumothorax with chest X-ray and there is no longer air being drained with a functioning ICC.

If the ICC is inserted to drain pleural fluid, the criteria for removal is not as clear. It is reported to be safe when less than 200-500ml is drained in 24 hours, however 300ml is the most commonly reported volume considered to be safe.[108,109] Some guidelines suggest a weight based volume of 15% of the total body lymph drainage, which is around 3.6ml/kg over a 24-hour period.[110] After a haemothorax, the removal threshold is often more conservative, with less than 200ml in 24 hours

considered to be safe.[111] It is considered safe to remove an ICC while a patient is receiving mechanical ventilation if they meet the criteria for removal.[111]

1.4.4.1 Technique for removal

The technique for ICC removal focuses on preventing air from being entrained into the pleural space. It involves removing the drain with a swift and gentle motion while simultaneously pinching the skin around the insertion site. This is then followed by applying an occlusive dressing; occasionally sutures or steri-strips are used to assist closure of the wound.[70,76] There has been debate about when in the respiratory cycle the catheter should be removed. The two main schools of thought are end-expiration or end-inspiration, with the breath held. A study that compared the two techniques in awake patients showed that there was no difference in post removal pneumothorax.[112] Another RCT[113] found a significant decrease in recurrent pneumothorax with end-expiration. However, many believe that in awake patients, it is the Valsalva manoeuvre (breath holding) which is important, and thus the recommendations are for consistency in practice of end-expiration or end-inspiration but ensuring breath holding, where possible.[110] This is different in unconscious mechanically ventilated patients, where ICC removal should occur at end-inspiration when the intrathoracic pressure is positive.[114]

1.5 Mechanical ventilation

Mechanical ventilation is a technique of using a device (ventilator) to support, partially or totally, the delivery of gas into the lungs. It is used to maintain adequate levels of oxygen and carbon dioxide in the blood and to reduce respiratory effort.[115,116] It can cover non-invasive ventilation (via a mask) and invasive ventilation (via an endotracheal tube or tracheostomy tube). For the purposes of this research, invasive ventilation only will be considered.

The indications for mechanical ventilation include respiratory failure (type one – hypoxia, and type two – hypercarbia), increased work of breathing, airway protection (e.g. decreased conscious state) to reduce the risk of aspiration, upper-airway obstruction, to assist sedation and neuromuscular paralysis (e.g. in the intensive care unit or during surgery), and in settings where ventilation control is necessary (e.g. controlling carbon dioxide levels in brain injuries).[117,118]

1.5.1 Physiological differences from normal breathing

Ventilation involves movement of the chest wall to produce a pressure gradient that will permit flow and movement of gas. This can be accomplished in spontaneous breathing by the respiratory muscles or by mechanical ventilation (positive pressure ventilation).[119] During spontaneous inspiration, negative intrathoracic, intrapleural and alveolar pressure is brought about by the contraction of respiratory muscles. The generation of negative pressure allows for gas to flow into the lungs. This is followed by expiration, which is generally a passive process but is occasionally assisted by respiratory muscles.[4,117,120] During positive pressure ventilation, inspiration occurs due to airway pressure being raised, leading to gas flowing down a pressure gradient into the lungs. This leads to positive intrathoracic, intrapleural and alveolar pressure. Expiration is again a passive process.[4,120,121] In summary, spontaneous breathing uses negative intrathoracic pressure and mechanical ventilation forces air into the lungs, causing relative positive pressure in the lungs and chest.

1.5.2 Changes in mechanical ventilation over time

Over the last 20 to 30 years, there have been changes in standard ventilatory settings. The main change is a decrease in the set tidal volume for all patients. A study in 2000[122] showed that mortality was lower in patients with ARDS (a severe inflammatory lung disorder) when lower tidal volumes (6ml/kg vs 12ml/kg) were used for ventilation. The findings of this study have been supported by a systematic review.[123] The results of the study in 2000 led to a change in practice, with decreased set tidal volumes used in the management of ARDS.[124,125]

Meta-analyses of the effect of decreased tidal volumes in mechanically ventilated patients without ARDS have shown decreased incidence of lung injury and lung infection when used in general anaesthesia[126], and decreased incidence of lung injury and decreased mortality when used in the ICU.[127] Due to this, it has become common practice in all mechanically ventilated patients to aim for a tidal volume of 6-8ml/kg ideal body weight.[128] Despite this being the aim, it is not always achievable due to overestimation of ideal body weight[129], concerns about ventilator dyssynchrony, and concerns about hypoventilation (hypercapnia and respiratory acidosis).[130]

1.5.3 Complications

There are a number of potential complications associated with mechanical ventilation; for the purposes of this review the focus will mainly be on respiratory complications. Respiratory complications include ventilator associated pneumonia (VAP) and ventilator-associated lung injury (which includes barotrauma, volutrauma, atelectotrauma, biotrauma and oxygen toxicity[131]). Ventilated patients have a higher risk of developing pneumonia due to reduced function of protective mechanisms (the lung's immune defences, swallowing, airway protective reflexes) and multiple risk factors associated with illness severity and ICU stay. The incidence of VAP is reported to be between 8% and 28%[132], and is increased in patients with severe underlying lung disease, aspiration pneumonia or pre-existing COPD.[38]

Ventilator-associated lung injury encompasses a group of complications which can be further subdivided. Barotrauma is damage to the lungs caused by sustained high pressure, which can lead to alveolar rupture, with air entering the pleural space causing pneumothorax and pneumomediastinum (air in mediastinal space).[4,133] Volutrauma is damage caused to the lungs by over-distension, which can particularly occur when a portion of the lung is receiving the majority of the tidal volume due to collapse of other areas. Volutrauma, like barotrauma, can also lead to pneumothorax and pneumomediastinum. It can also manifest as pulmonary oedema due to increased alveolar membrane permeability.[4,131,134] Atelectotrauma is associated with repeated recruitment and collapse of alveoli, leading to oedema and lung inflammation. Biotrauma, thought to be associated with volutrauma and atelectotrauma, is due to a proinflammatory response to ventilation, leading to lung inflammation via activation of immunological and coagulation systems.[4,131,135] A proinflammatory response leading to tissue damage and cell death can also occur in response to high levels of inspired oxygen, which is caused by oxygen free radicals and reactive oxygen species.[136] The exact level at which this damage occurs is unknown and likely to be different for each patient.

Although it has been shown that these complications can occur due to mechanical ventilation, they can also be due to the underlying lung pathology necessitating the need for mechanical ventilation. Distinguishing the cause of the complication can be difficult and often the cause is left unknown.

Non-respiratory complications include decreased venous return, leading to decreased cardiac output, salt and water retention due to decreased renal blood flow, increased intracranial pressure, sleep disturbance, delirium and discomfort.[117,134]

1.6 Significance of the review

Currently, there is a lack of consensus between guidelines, literature and specialist opinion on how to manage mechanically ventilated patients with occult pneumothoraces. Across the world, there is increasing utilisation of conservative management in some facilities, however there are still ongoing variations between hospitals and specialists regarding the correct management strategy.

The aim of the research presented in this thesis was to conduct a systematic review to establish the effectiveness of conservative management and determine the incidence of complications in both conservative management and ICC insertion in mechanically ventilated patients with traumatic occult pneumothorax. Combining all available data on this topic will allow clinicians to make more informed decisions on management and may allow for more concise recommendations in the guidelines and teaching resources.

1.7 Review objective and question

The review objective was to locate, critically appraise and synthesise the best available evidence on the effectiveness and safety of conservative management of traumatic occult pneumothoraces in mechanically ventilated patients.

The specific review question was:

In the mechanically ventilated patient, is conservative management safe and effective for the management of traumatic occult pneumothorax when compared to insertion of a prophylactic intercostal catheter?

1.8 Methodology overview

A systematic review is a comprehensive summary of all available evidence relevant to a specific question.[137] Systematic reviews are regarded as the highest level of

evidence and therefore often used for guideline development, as the risk of bias is minimised due to the explicit methods used.[138-141]

The process involved for a systematic review includes the following steps[137,142-145]:

1. Formulation of a review question
    a. Often formulated using PICO (population, intervention, comparison and outcome) concepts, with keywords and synonyms extrapolated from this.[138]
2. Development of an *a priori* study protocol (the study protocol for this systematic review was published in 2019[146])
    a. Including predetermined inclusion and exclusion criteria, clear explanation of the planned search, how evidence will be critically appraised and synthesised.
    b. Development of a comprehensive search strategy.
3. Locating the evidence
    a. Searching of predefined databases using appropriate database headings and field terms.
    b. Searching for grey/unpublished data.
    c. Hand searching reference lists of included evidence.
    d. The search should be reported and reproducible.
4. Assessing the methodological quality of included studies
    a. Critically appraising to ascertain risk of bias.
5. Synthesising the evidence
    a. This is often done using meta-analysis (statistical method that combines the results from different studies, and providing an overall effect estimate of the intervention[137,147]).
6. Interpreting the findings
    a. Exploring reasons for heterogeneity of results across a study.

There are two major advantages of systematic reviews over clinical trials. Combining the data from a number of studies increases the statistical power, which increases the probability of identifying a true effect, if one is present. This is particularly useful for interventions with rare adverse outcomes or where data are sparse, which is the case in the management of occult pneumothoraces. The second

advantage is that systematic reviews produce generalisability through demonstrating similar effects over a variety of clinical settings and countries.[148] Generalisability of adverse effects and treatment harms can be further shown with the addition of observational research. Observational research has been shown to have no difference to RCTs in estimates of risk of adverse events, and therefore provides essential data when investigating adverse events and treatment harms.[149,150]

Chapter 2: Methods

This chapter presents the methods used in the conduct of the systematic review, incorporating the inclusion criteria, search strategy, methods for critical appraisal, data extraction and synthesis.

An *a priori* study protocol was completed and published to guide the conduct of this systematic review[146] (see also Appendix 1). This review adheres to the JBI methodology for systematic reviews of effectiveness.[143]

2.1 Inclusion criteria

2.1.1 Participants

The review considered studies that included stable patients of any age, diagnosed with a traumatic occult pneumothorax on thoracoabdominal CT scan, who have undergone mechanical ventilation. The mechanical ventilation could occur in the emergency department, intensive care unit or as part of the provision of general anaesthesia.

All ages were included as the management of occult pneumothorax is similar in adults and paediatric patients. There may be differences in how their ventilation is managed, however there is also no standard ventilation mode in adult patients throughout ICU and anaesthetics, therefore inclusion occurred irrespective of these potential differences.

Including only stable patients is important as an unstable patient with a known or suspected pneumothorax would receive bilateral ICCs as part of the management of their instability to rule out tension pneumothorax as a potential cause, thereby making conservative management impossible.

The review considered occult pneumothoraces caused by either blunt or penetrating trauma, as the mechanism causing the pneumothoraces is similar. Details of the mechanisms can be found in 'Introduction' (see Section 1.2.4.3).

Occult haemopneumothoraces were excluded from the review as the haemothorax would add further confounding factors to the review. This is due to the increased risk of ICC insertion and empyema with haemothorax present.

2.1.2 Intervention of interest

The review considered studies that evaluated conservative management for occult pneumothorax. Conservative management includes clinical observation, serial examination and/or serial chest X-ray.

2.1.3 Comparator

The review considered studies that compared the intervention to ICC insertion for occult pneumothorax. The ICC can be inserted via any method, including the Seldinger technique or blunt dissection (see Section 1.4.1).

2.1.4 Types of studies

The review considered both experimental and quasi-experimental study designs, including RCTs and non-RCTs. In addition, comparative observational studies, including prospective and retrospective cohort studies, were considered for inclusion. Observational data was included as it is essential to provide a full picture when investigating harms and adverse effects of treatment.

2.2 Outcomes

2.2.1 Primary outcomes

The primary outcomes of interest were progression of pneumothorax (seen on chest X-ray), ICC insertion for any reason, incidence of tension pneumothorax (diagnosed clinically) and incidence of pneumonia/empyema.

2.2.2 Secondary outcomes

The secondary outcomes of interest were all-cause mortality, ICC insertion (tension pneumothorax), ICC insertion (progression to simple pneumothorax), ICC insertion (non-pneumothorax reasons), length of stay in hospital and intensive care (in days), duration of mechanical ventilation (in days), duration of ICC dwelling (in days), haemodynamic instability (measured as need for vasopressor support), pain (measured by a validated pain scoring tool for sedated ICU patients such as Behavioural Pain Scale [BPS] and Critical-Care Pain Observation Tool [CPOT]),[151,152] and analgesia requirements (measured in parenteral morphine equivalents per 24 hours as per Australian and New Zealand College of Anaesthetists [ANZCA] opioid conversion[153]).

This review also considered adverse events/complications of ICC insertion (measured as composite and breakdown, including malpositioning, infection, organ injury and vascular injury).

2.3 Review method

2.3.1 Search strategy

The search strategy followed a three-step approach and aimed to locate both published and unpublished studies.[143] This process commenced in February 2019. Step 1 involved an initial limited search of PubMed (MEDLINE) to identify articles on the topic, using the terms "occult pneumothorax" AND "mechanical ventilation". The text words contained in the titles and abstracts of relevant articles were analysed. In addition, the index terms used to describe the articles were reviewed and relevant MeSH terms (PubMed's controlled vocabulary thesaurus) were searched for. The key text words and MeSH terms were then used to develop a full search strategy for PubMed. The final step was to adapt the PubMed search strategy, including all identified keywords and index terms, for the following databases: Embase, CINAHL (EBSCO), Web of Science and Cochrane Central Register of Controlled Trials. Sources of unpublished studies were searched for in the following registries: International Clinical Trials Registry (ICTR), Australian and New Zealand Clinical Trials Registry (ANZCTR) and ClinicalTrials.gov. The full search strategy was completed on 17th June 2019. There were no date or language limits applied to the search. Details of the searches conducted in each database and registry are detailed in Appendix 2. This includes logic grids and full search strategies. Finally, the reference lists of all studies selected for inclusion were screened for additional studies.

2.3.2 Study selection

Following the search, all identified records were collated and uploaded into Endnote X8.2 (Clarivate Analytics, PA, USA)[154] and duplicates removed. Titles and abstracts were then screened twice by one reviewer (JS) for assessment of eligibility, according to the inclusion criteria for the review. Potentially relevant studies were retrieved in full and their citation details imported into the JBI System for the Unified Management, Assessment and Review of Information (JBI

SUMARI2017) (JBI, Adelaide, Australia).[155] The full texts of selected citations were assessed in detail against the inclusion criteria by one reviewer (JS), and uncertainties that arose during inclusion were resolved through discussion with a second and third reviewer (PS, EA). Reasons for exclusion of full text studies that did not meet the inclusion criteria were recorded (see Appendix 3).

2.3.3 Assessment of methodological quality

Eligible studies were critically appraised by two independent reviewers (JS, AV) at the study level for methodological quality in the review using standardised critical appraisal instruments from JBI for experimental and comparable cohort studies[143] (see Appendix 4). Nine authors of papers that were published within the last ten years (i.e. after 2009) were contacted to request missing or additional data for clarification (see Appendix 5). Disagreements that arose between reviewers were resolved through discussion. A decision was made *a priori*[146] (see Appendix 1), given the expected limited quantity of research in this field, to not exclude studies based on low methodological quality and high risk of bias, rather, all studies were included to ensure full consideration of the available dataset in subsequent analyses.[156]

2.3.4 Data extraction

Data were extracted from studies included in the review using a modified standardised data extraction tool[143] (see Appendix 6). The data extracted included specific details about the population (age, sex and injury severity score [ISS]), study methods, and the intervention and comparator (including insertion technique, where possible), and outcomes of significance to the review objective (see Section 2.2). Nine authors of papers that were published within the last ten years (i.e. after 2009) were contacted to request missing or additional data (see Appendix 5).

2.3.5 Data synthesis

Selection of an appropriate meta-analytical model was complicated due to the sparse data and rare events observed for the majority of outcomes. When there are zero event counts in studies, the Mantel-Haenszel (M-H) model requires the use of a continuity correction (default is 0.5 in most statistical software); this has a marked impact where there is sparse data throughout an analysed dataset leading to a biased calculated effect size.[157,158] The Peto odds ratio (POR) method is well suited to rare

events (<1%) as it does not require a continuity correction for single arm zero event studies, however it does not perform well when there is an imbalance in the number of participants between groups[157-159] (which is common with observational studies). To maintain the same meta-analytical model that could account for sparse data and the presence of zero values and unbalanced groups throughout all the analyses, a logistic regression model was chosen after discussion with statisticians (KH, JL, JB). Logistic regression has been shown to perform well with rare events and also with group imbalance[157-159] and does not require continuity correction.

Studies, where possible, were pooled in statistical meta-analysis using Stata V15 (Stata Corp LLC, Texas, USA).[160] Effect sizes were expressed as odds ratios and their 95% confidence intervals calculated for analysis. A mixed-effects logistic regression model using a one stage approach was used for the meta-analysis[161-163]; this model takes into account heterogeneity between studies when using a one stage approach.[161,164] The impact of the chosen model on the effect size estimate was explored using sensitivity analyses.[163] Other models used included the M-H random effects model and POR for RCT data, as the data from RCTs were balanced and had less zero events. For cohort studies, the M-H fixed-effects model and POR were used as there was a lower incidence of events in the cohort studies and many of the cohort studies were unbalanced. The M-H fixed-effects model was used for cohort studies, as the random-effects model has been shown to produce biased effect sizes when there are rare or sparse data.[159] Analyses with the M-H and POR models were performed with RevMan V5.3 (Copenhagen: The Nordic Cochrane Centre, Cochrane).[165] Heterogeneity for M-H and POR was assessed statistically using the standard $\chi^2$and I^2 test. The logistic regression, M-H and POR odds ratios, and 95% confidence intervals were presented together, where possible, for each outcome to aid visual inspection of the results of the various methods used for data analysis.

Meta-analysis of experimental and observational data were completed separately for each outcome. In all analyses, raw event counts were utilised as adjusted estimates were not provided. Impact of sample size and event counts, that is, studies that appeared to have a marked influence in terms of their contribution to the overall effect in any analysis, were explored using sensitivity analysis. A funnel plot was not generated as there were less than 10 studies in all the meta-analyses.[166] Any study that did not have complete data for a given outcome was not included in the

meta-analysis for that outcome; rather, the available study results were included in a narrative summary, where appropriate. The study by Fulton & Bratu[167] was not included in the statistical analysis as their planned 'ICC group' had no patients to include; it has been included in the narrative summary. Where statistical pooling was not possible, the findings are presented in narrative form, including tables and figures to aid in data presentation, where appropriate.

2.3.6 Assessing certainty in the findings

Due to the paucity of data and the required analyses necessitating calculation of the odds ratio, assessment of certainty in the findings using Grading of Recommendations Assessment, Development and Evaluation (GRADE) processes, including Summary of Findings tables, was not progressed as intended *a priori*.[146]

Chapter 3: Results

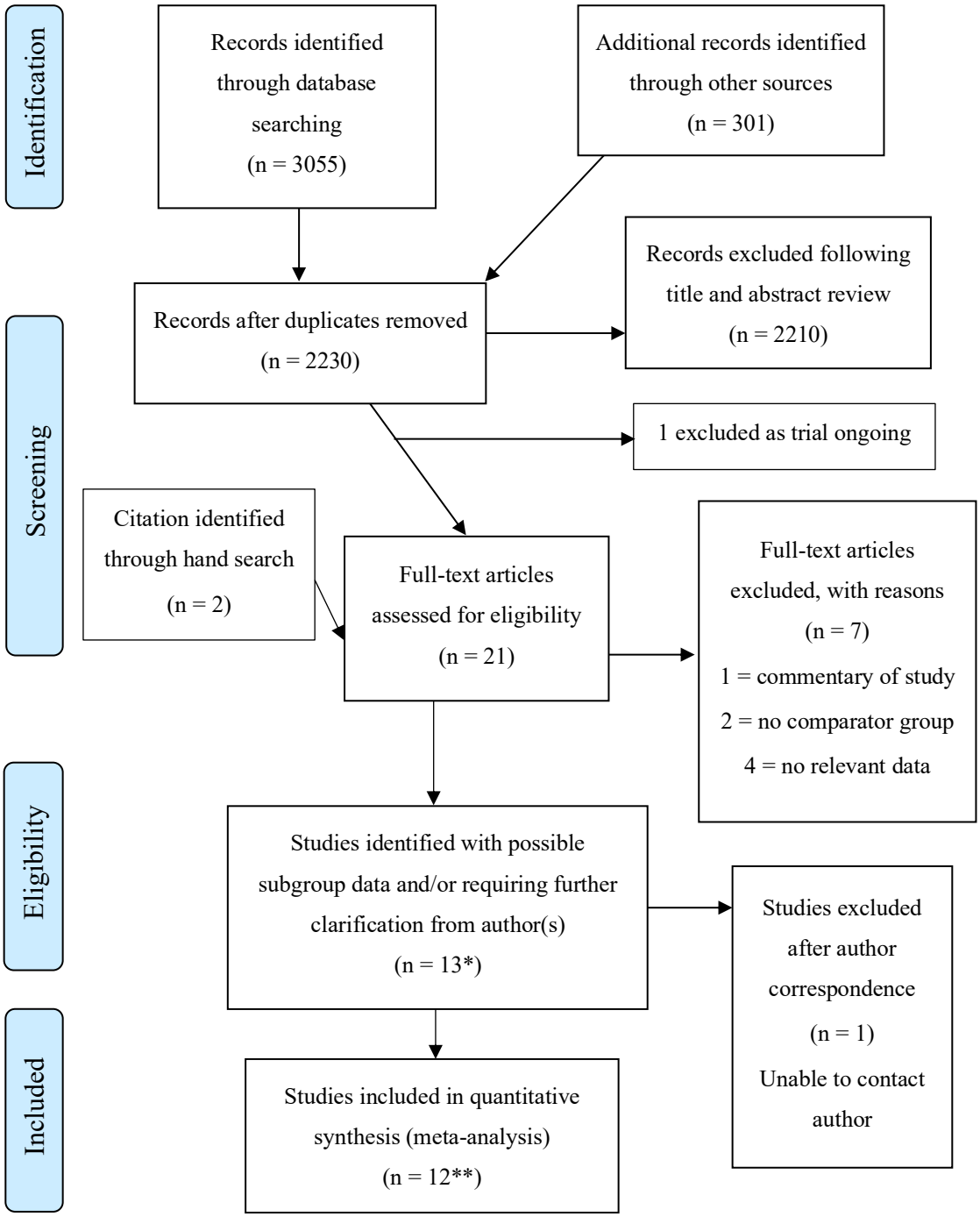
This chapter presents the results of the systematic review. It includes results of the search processes, study selection, assessment of methodological quality and characteristics of included studies. The findings for each outcome are also reported in this chapter.

3.1 Searching and study selection

The search for published studies returned a total of 3055 citations from the following databases (PubMed 595; Embase 1694; Cochrane Central Register of Controlled Trials 103; Web of Science 566; CINAHL 97). A search of clinical trial registries to locate additional unpublished studies returned 301 citations (ClinicalTrials.gov 110; International Clinical Trials Registry (ICTR) 104; Australian and New Zealand Clinical Trials Registry (ANZCTR) 87). From these citations, 1126 duplicates were identified and removed (see Figure 3.1).

The titles and abstracts of the remaining 2230 unique citations were screened twice against the inclusion criteria (see Section 2.1). This led to 2210 citations being excluded, leaving 20 citations for full-text retrieval and review. One of these initial 20 citations was unavailable as the trial was still ongoing.[168] Two further articles[169,170] of interest were identified from hand searching the reference lists of the 19 full text articles. Overall, 21 full text articles were assessed for eligibility. Seven of the 21 articles were excluded following full-text review (see Figure 3.1 and Appendix 3). One of the articles[171] was a pilot of a later published study[65]; the participants were included in the later study. Data from this article[171] has been combined with the later study[65] and treated as one record. One article[172] was a commentary of a previously published RCT. Two studies were excluded[64,173] as they had no planned comparator group, whereas four were excluded as they did not report pertinent data (Johnson[174] – no occult pneumothoraces, Lamb et al.[175] – no ventilated patients in observation group, Kaiser et al.[176] – management and outcomes not included, Wolfman et al.[177] – relevant data missing). One further article[178] was excluded following attempts to contact the authors were unsuccessful (see Appendix 5), and as the published data did not include defined occult pneumothoraces. Overall, 12 studies were included (13 articles), comprising three RCTs and nine

cohort studies (two prospective and seven retrospective), with a total of 311 participants (135 in the RCTs and 176 in the cohort studies) (see Figure 3.1).



** 13 studies/14 publications*
***12 studies/13 publications*

Figure 3.1: PRISMA flow diagram of the study selection and inclusion process

3.2 Methodological quality of included studies

The methodological quality of the included studies is presented in Table 3.1 for RCTs and Table 3.2 for cohort studies. An 'unclear' rating indicates that the relevant details could not be found in the articles and the data could not be ascertained (either due to the author being uncontactable or unable to provide additional information, or the article having been published over 10 years ago) (see Section 2.3.3 and Appendix 5).

Of the three included RCTs, it was clear in two trials[63,65] that appropriate randomisation was used and that allocation was concealed (Table 3.2, Questions 1 and 2). Brasel et al.[179] provided insufficient detail about how they randomised patients and how allocation was concealed. Treatment groups were similar in two studies[65,179] (Table 3.2, Question 3); Enderson et al.[63] had differences in sex (conservative management group 77% male versus 95% in ICC group) and age (mean age 35.8 ± 4.0 in conservative management group versus 39.4 ± 3.7 in ICC group). Due to the nature of the intervention, none of the trials could blind either patient or clinician (Table 3.2, Questions 4 and 5). It was unclear in all three studies[63,65,179] if assessors were blinded to treatment allocation (Table 3.2, Question 6). It was clear in Kirkpatrick et al.[65] that treatment groups were treated identically other than the intervention of interest. In Enderson et al.[63] it was unclear if there were differences in treatment of the two groups other than the intervention of interest. In the study by Brasel et al.[179], the two groups were treated differently. The conservative management group had signs above their bed stating they had an undrained pneumothorax (Table 3.2, Question 7). Follow-up was complete in all three studies[63,65,179] (Table 3.2, Question 8). All participants[63,65,179] were analysed in the groups to which they were allocated (Table 3.2, Question 9). It was unclear in two studies[63,179] if outcomes were measured the same way in both groups and in a reliable way. Brasel et al.[179] and Enderson et al.[63] did not state how they measured progression of pneumothorax (Table 3.2, Questions 10 and 11). Appropriate statistical analysis was completed in all three trials[63,65,179] (Table 3.2, Question 12). All three trials[63,65,179] had appropriate study designs (Table 3.2, Question 13). Two RCTs[63,179] rated low (5 and 6 out of 13) due to the uncertainty of many questions which were not clarified with the authors due to the time lapse since publication of

the articles. The study by Kirkpatrick et al.[65] had more clarity in the reporting of its methodology due to the standardised reporting of RCT methods based on the Consolidated Standards of Reporting Trials (CONSORT) guidelines[180], which facilitated assessment of the conduct of the trial and thus was rated 10 out of 13 for methodological quality.

Table 3.1: Methodological quality of randomised controlled trials included in this review

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Total
Brasel et al.[179]	U	U	Y	N	N	U	N	Y	Y	U	U	Y	Y	5
Enderson et al.[63]	Y	Y	N	N	N	U	U	Y	Y	U	U	Y	Y	6
Kirkpatrick et al.[65]	Y	Y	Y	N	N	U	Y	Y	Y	Y	Y	Y	Y	10
Total Y score (%)	66.6	66.6	66.6	0.0	0.0	0.0	33.3	100	100	33.3	33.3	100	100	

Studies are rated as Yes (Y), No (N) or Unclear (U) for each question. See Appendix 4 for explanatory details of critical appraisal tools.

Appraisal questions for randomised controlled trials (RCTs):

1. Was true randomisation used for assignment of participants to treatment groups?
2. Was allocation to treatment groups concealed?
3. Were treatment groups similar at baseline?
4. Were participants blind to treatment assignment?
5. Were those delivering treatment blind to treatment assignment?
6. Were outcome assessors blind to treatment assignment?
7. Were treatment groups treated identically other than the intervention of interest?
8. Was follow up completed and if not, were differences between groups in terms of their follow up adequately described and analysed?
9. Were participants analysed in the groups to which they were randomised?
10. Were outcomes measured in the same way for treatment groups?
11. Were outcomes measured in a reliable way?
12. Was appropriate statistical analysis used?
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomisation, parallel groups) accounted for in the conduct and analysis of the trial)

For cohort studies, there were two prospective and seven retrospective studies. Six[16,170,181-184] had similar populations. Fulton & Bratu[167] did not recruit any patients for their planned ICC group. Zhang et al.[10] and Collins et al.[169] reported a significant difference in the age of patients in the two groups (Zhang: conservative management 25 years mean age versus ICC 34 years mean age, $p = 0.027$; Collins: conservative management median 24 years versus ICC median 44.5years) (Table

3.1, Question 1). The exposure was measured in a consistent and reliable way in all cohort studies[10,16,167,169,170,181-184] (Table 3.1, Questions 2 and 3). In seven studies[10,16,167,170,182-184], it was clear if confounding factors had been identified (Table 3.1, Question 4), with five[10,167,170,183,184] explaining how they dealt with these confounding factors (Table 3.1, Question 5), however the studies did not adjust effect estimates for the stated confounding factors. Participants in all the studies[10,16,167,169,170,181-184] were free of the outcome at the beginning of the study (Table 3.1, Question 6). Seven studies[10,167,170,181-184] were clear on how they measured outcomes and did so in a reliable way (Table 3.1, Question 7). Seven studies[10,167,170,181-184] stated their follow-up times (Table 3.1, Question 8) and eight[10,167,169,170,181-184] stated their follow-up rates (Table 3.1, Question 9). It was clear in three studies[10,167,182] how loss to follow-up was addressed (Table 3.1, Question 10). In eight studies[10,16,169,170,181-184], appropriate statistical methods were used (Table 3.1, Question 11). Overall, five[10,170,182-184] of the nine cohort studies were rated 10 out of 11 for methodological quality.

Table 3.2: Methodological quality of cohort studies included in this review

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Total
Ball et al.[170]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	10
Collins et al.[169]	N	Y	Y	U	U	Y	U	U	Y	U	Y	5
Fulton & Bratu[167]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	9
Holmes et al.[181]	Y	Y	Y	U	U	Y	Y	Y	Y	N	Y	8
Lee et al.[16]	Y	Y	Y	Y	U	Y	U	U	U	U	Y	6
Llaquet Bayo et al.[182]	Y	Y	Y	Y	U	Y	Y	Y	Y	Y	Y	10
Notrica et al.[183]	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	10
Wilson et al.[184]	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	10
Zhang et al.[10]	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10
Total Y score (%)	66.6	100	100	77.7	55.5	100	77.7	77.7	88.8	33.3	88.8	

Studies are rated as Yes (Y), No (N) or Unclear (U) for each question. See Appendix 4 for explanatory details of critical appraisal tools.

Appraisal questions for cohort studies:

1. Were the two groups similar and recruited from the same population?
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?
3. Was the exposure measured in a valid and reliable way?
4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?
7. Were the outcomes measured in a valid and reliable way?
8. Was the follow up time reported and sufficient to be long enough for outcome to occur?
9. Was the follow up complete, and if not, were reasons to los to follow up described and explored?
10. Were strategies to address incomplete follow up utilised?
11. Was appropriate statistical analysis used?

3.3 Characteristics of included studies

3.3.1 Study populations

Details of the participants' baseline characteristics (age, sex and injury severity score [ISS]) are presented in Table 3.3. Non-statistically significant differences

were seen in the baseline characteristics of the following cohort studies. Collins et al.[169] (age: conservative management median 24 versus ICC median 44.5), Llaquet Bayo et al.[182] (ISS: conservative management median 33 versus ICC median 38.5, *p*-value 0.245) and Wilson et al.[184] (age: conservative management median 44 versus ICC median 29, *p*-value 0.17). Statistically significant differences were seen in the baseline characteristics of Zhang et al.[10] (age: conservative management median 25 versus ICC median 34, *p*-value 0.027). Other than the above differences, all study populations were similar at baseline between the two groups (see Table 3.3).

Table 3.3: Baseline characteristics of study populations

Study	Group	Age, years	Male sex, n (%)	ISS
Ball et al.[170]	Conservative Mx	Not specified	Not specified	Not specified
	ICC	Not specified	Not specified	Not specified
Brasel et al.[179] *	Conservative Mx	37.5 (average)	Not specified	19.14 (average)
	ICC	39.5 (average)	Not specified	22.41 (average)
Collins et al.[169]	Conservative Mx	24 (22-35) median (IQR)	4 (66.6%)	29 (24-30) median (IQR)
	ICC	44.5 (21-59) median (IQR)	4 (57%)	33 (26-41) median (IQR)
Enderson et al.[63] *	Conservative Mx	35.8 ± 4.0 (16-88) Mean ± SEM (range)	17 (77.2%) Number (%)	26.3 ± 2.7(9-66) Mean ± SEM (range)
	ICC	39.4 ± 3.7 (19-79) Mean ± SEM (range)	18 (94.7%) Number (%)	26 ± 2.5 (10-50) Mean ± SEM (range)
Fulton & Bratu[167]	Conservative Mx	13.3 (2-17) Mean (range)	54.4%	34.9 (16-66) Mean (range)
Holmes et al.[181]	Conservative Mx	Not specified	Not specified	Not specified
	ICC	Not specified	Not specified	Not specified
Kirkpatrick et al.[65]	Conservative Mx	33 (25.0 – 48.0) median (IQR)	34 (68%) Number (%)	34 (22-43) Median (IQR)
	ICC	29.5 (22.0-45.0) median (IQR)	27 (67.5%) Number (%)	36 (27-43) Median (IQR)
	p -value	0.344	1.00	0.271
Lee et al.[16] *	Total	45 (2-91) Mean (range)	32 (89%)	24 median
Llaquet Bayo et al.[182]	Conservative Mx	32.2 (25.7-49.4) median (IQR)	Not specified	33 (17-41) median (IQR)
	ICC	36.9 (29.9-55.6) median (IQR)	Not specified	38.5 (29-57) median (IQR)
	p -value	0.559		0.245
Notrica et al.[183]*	Total	11.6 ± 5.9 Average	Not specified	22.5 ± 10.9 average
Wilson et al.[184]*	Conservative Mx	44 (24-54) median (IQR)	22 (66%)	22 (14-29) median (IQR)
	ICC	29 (19-51) median (IQR)	27 (77%)	24 (19-33) median (IQR)
	p -value	0.17	0.34	0.10
Zhang et al.[10]*	Conservative Mx	25 Median	37 (77%)	18.5 Median
	ICC	34 median	31 (88%)	17 Median
	p -value	0.027	0.251	0.436

ISS – injury severity score; Mx – management; ICC – intercostal catheter, IQR – interquartile range, SEM – standard error of mean

** Characteristics of whole study population, not specific to ventilated subgroup of patients*

The three RCTs[63,65,179] included adults only. Of the nine cohort studies, three[167,181,183] included only paediatric patients, one included only adults[182], one[169] did not specify the age range, and four[10,16,170,184] included all ages (see Table 3.4).

Two RCTs[63,65] included patients with blunt and penetrating trauma, the remaining RCT[179] excluded patients with penetrating trauma. Five cohort studies included only blunt trauma[10,16,169,181,184] and four included both blunt and penetrating trauma[167,170,182,183] (see Table 3.4). One RCT[65] recruited only mechanically ventilated patients, while two[63,179] recruited patients regardless of their mechanical ventilation status, and recruited a proportion of mechanically ventilated patients within both arms of the studies.

One cohort study[167] included only mechanically ventilated patients, the remaining eight[10,16,169,170,181-184] included patients receiving mechanical ventilation and patients who were breathing without mechanical support (see Table 3.4).

3.3.2 Geographical location

Two RCTs were conducted in the USA[63,179] and one in Canada.[65] The majority of cohort studies (six out of nine) were conducted within North America (three in Canada[167,170,184] and three in the USA[169,181,183]). The three trials conducted outside of North America were in Hong Kong[16], Singapore[10] and Spain[182], respectively. Further details indicating the hospitals in which the studies were performed can be found below (see Table 3.4). Two trials were multicentre RCTs[65,179] and Enderson et al.[63] recruited patients from one hospital. Two cohort studies[183,184] collected data from multiple hospitals, the remaining seven[10,16,167,169,170,181,182] collected data from single sites (see Table 3.4).

Table 3.4: Characteristics of included studies

Study	Setting/ context	Participant characteristics	Participants	Outcomes measured	Description of main results/ author's conclusion	Comments
Ball et al. 2005[170]	**Study Design:** Retrospective cohort study **Country:** Canada **Site:** Level 1 trauma centre, single centre **Time period:** June 2002 - July 2003	**Inclusion criteria:** All trauma patients with ISS >12, who had CT scan showing occult PTX **Age:** All ages **Insertion technique:** Blunt dissection with 28 or 32F ICC **Trauma type:** Blunt and penetrating **CT scanner:** Chest/abdomen/pelvis or abdomen/pelvis, LightSpeed QZ/I-plus scanner with 5mm slices	**Total:** 49 patients with occult PTX ICC group: 23 Conservative Mx group: 26 **Ventilated subgroup**: ICC group: 13 Conservative Mx group: 4	ICC placement ICU and hospital length of stay Ventilation days Size of chest tube Chest tube complications Pulmonary complications	No serious complications resulted from conservative Mx, however 2 patients in the conservative Mx group required an ICC for progression of PTX. 22% of patients with ICCs had tube related complications or required repositioning. Authors concluded that due to ICC insertion often having adverse consequences, rethinking an algorithmic policy of prophylactic thoracostomy is crucial.	**Ventilated subgroup:** In the conservative Mx group there was one patient requiring ICC insertion for progression of PTX. In the ICC group there were 3 complications (1 malpositioning and 2 vascular injuries).

					Occult PTX incidence: 15% (49/338) in all seriously injured patients who had thoraco-abdominal CT scans, 6% (49/751) among all trauma registry patients.	
Brasel et al. 1999[179]	**Study Design:** Randomised controlled trial **Country:** USA **Site:** Multicentre (2 centres) **Time period:** Jan 1995 - Dec 1997	**Inclusion criteria:** All blunt trauma patients with occult PTX seen on abdominal CT **Age:** Over 18 years **Insertion technique:** 36F blunt dissection **Trauma type:** Blunt only **CT scanner:** Abdominal, General Electric HiSpeed Advantage 10mm slices	**Total:** 39 patients with 44 occult PTX ICC group: 18 Conservative Mx group: 21 **Ventilated subgroup:** ICC group: 9 Conservative Mx group: 9	Respiratory distress PTX progression Pneumonia Retained haemothorax Placement of ICC Length of stay Ventilator days	No difference in overall complication rate. No patient had respiratory distress related to the occult PTX or required emergent ICC placement. 20% of patients conservatively managed required chest tube placement. Authors concluded that conservative Mx is safe regardless of the need for mechanical ventilation.	**Ventilated subgroup:** PTX progression occurred in 2 patients in the conservative Mx group (requiring ICC placement) and 3 patients in ICC group (not requiring further ICC). No tension PTX in either group. **Reason for ventilation:** 3 patients in each group had ventilation for procedure only.

		Ventilation settings: TV 8-10ml/kg Peak pressure limits 30-35 mmHg			**Occult PTX incidence:** 5.9% (98/1669) receiving abdominal CT scan, 1.9% (98/5126) among all blunt trauma patients.	6 in each arm ventilated for greater or equal to 1 day.
Collins et al. 1992[169]	**Study Design:** Retrospective cohort study **Country:** USA **Site:** Level 1 trauma centre (University of California Irvine Medical Centre) **Time period:** not specified	**Inclusion criteria:** Trauma patients undergoing CT scanning of abdomen and pelvis within 1 hour of arrival showing occult PTX **Age:** Not specified **Insertion technique:** "Standard fashion" **Trauma type:** Blunt only **CT scanner:** Abdomen/pelvis, model not specified	**Total:** 26 patients with 27 occult PTX ICC group: 13 Conservative Mx group: 14 **Ventilated subgroup:** ICC group: 6 Conservative Mx group: 7	Hospital and ICU length of stay ICC dwell time Complications Mortality	Identified 2 significant complications of ICC insertion (intercostal artery laceration and self-removal). Conservative Mx produced 2 complications (one delayed PTX and one delayed haemothorax with possible delayed PTX), both resolved with placement of ICC. No patient developed tension PTX. 2 patients died, both considered unrelated to ICC or occult PTX.	**Ventilated subgroup:** There was one patient in each group requiring ICC placement (ICC group: progression of PTX due to self-removal of ICC, conservative Mx group: non-PTX related reasons). 1 patient in each group died.

Enderson et al. 1993[63]	**Study Design:** Randomised controlled trial **Country:** USA **Site:** Single centre, University of Tennessee Medical Centre **Time period:** Oct 1990 - May 1992	**Inclusion criteria:** Trauma patients undergoing abdominal CT showing occult PTX **Age:** "Adult" **Insertion technique:** Blunt dissection 36F **Trauma type:** Blunt and penetrating **CT scanner:** Abdominal scans, model not specified	**Total:** 40 occult PTX ICC group: 19 Conservative Mx group: 21 **Ventilated subgroup:** ICC group: 12 Conservative Mx group: 15	Major complications: Progression of PTX Empyema Pneumonia Minor complications: Atelectasis Hospital and ICU length of stay	9 patients had complications in conservative Mx group (8 progression of PTX including 3 tension PTX, 1 pneumonia, 1 empyema, 3 atelectasis) and 8 patients in ICC group (1 pneumonia, 8 atelectasis). All progression of PTX happened to patients receiving mechanical ventilation. Authors concluded the results suggested that patients with occult PTX requiring mechanical ventilation are at significant risk for progression of their PTX and development of tension PTX. Therefore, ICC should be used in all patients with occult PTX requiring mechanical ventilation.	**Ventilated subgroup:** In conservative Mx group 8 patients had progression of PTX requiring ICC placement (including 3 tension PTX), 1 developed empyema following insertion of an ICC for progression of PTX. No PTX progression occurred in ICC group. **Reason for ventilation:** All 15 in conservative Mx group and 10 out of 12 in the ICC group had an operation. However not stated if ventilation was required pre/post operation.

					Occult PTX incidence: 5.6% (40/709) receiving abdominal CT scan, 1.2% (40/3261) among all blunt trauma patients.	
Fulton & Bratu 2015[167]	**Study Design:** Retrospective cohort study **Country:** Canada **Site:** Single centre, Stollery Children's hospital **Time period:** Jan 2001 - Dec 2011	**Inclusion criteria:** Mechanically ventilated, ISS score >12 and a diagnosis of PTX (presence of occult PTX determined with chart review) **Age:** 0-17 years **Insertion technique:** Unspecified **Trauma type:** Blunt and penetrating to be included (however all patients had blunt) **CT scanner:** Abdomen +/- thorax, unspecified model	**Total:** ICC group: 0 Conservative Mx group: 19 (15 children)	Placement of ICC Progression of PTX Complications	All patients were successfully managed without the need for ICC. Authors concluded results suggest that occult PTX in paediatrics can be managed without ICC. **Occult PTX Incidence:** 3.8% (19/496) children admitted to paediatric ICU and receiving MV.	There was no progression of PTX and no ICC insertions required in the conservative Mx group. **Reason for ventilation:** 6 of 19 patients had less than 24 hours ventilated.

Holmes et al. 2001[181]	**Study Design:** Prospective cohort study **Country:** USA **Site:** Single centre, Level 1 trauma centre **Time period:** over 28-month period	**Inclusion criteria:** Blunt trauma patients undergoing abdominal CT **Age:** Under 16 years **Insertion technique:** Unspecified **Trauma type:** Blunt only **CT scanner:** Abdominal scans, either 4th generation Toshiba-900 (5mm slices) or helical CTi by General Electric (3mm if <10kg, 5mm if 10-50kg, 7mm if >50kg)	**Total:** 12 occult PTX (11 patients) ICC group: 1 Conservative Mx group: 11 **Ventilated subgroup:** ICC group: 1 Conservative Mx group: 2	Respiratory compromise Haemodynamic compromise ICC placement	Incidence of occult PTX in paediatric blunt trauma is low. ICC is infrequently required for occult PTX. Further RCT required. **Occult PTX incidence:** 2.2% (12/538) children undergoing abdominal CT scan.	**Ventilated subgroup:** No patient in either group had respiratory or haemodynamic compromise or need for ICC placement.
Kirkpatrick et al. 2013[65]	**Study Design:** Randomised controlled trial **Country:** Canada	**Inclusion criteria:** Patients with occult PTX identified on CT **Age:** Over 18 years **Insertion technique:**	**Total:** ICC group: 40 Conservative Mx group: 50	Primary outcome: Composite variable denoting respiratory distress (defined as acute change from a "stable" baseline clinical state that	15% ICC complication and 15% had suboptimal ICC positioning. Risk of respiratory distress was similar between two groups.	ICC insertion was required in 10 patients in conservative Mx group (1 tension PTX, 3 progression to simple PTX, 6 for non-PTX related reasons) and in 7 patients in ICC group

	Site: Multicentre, Regional trauma centres **Time period:** Oct 2006 - Feb 2012	Blunt dissection or Seldinger technique **Trauma type:** Blunt and penetrating **CT scanner:** Any site, model not specified		required the urgent placement of an ICC, an acute increase by 0.2 FiO2, requirement for pharmacological paralysis to improve ventilator synchrony, requirement for manual bag-mask ventilation or prone ventilation, or documentation of an adverse respiratory event in the medical record) Secondary outcomes were divided into respiratory related (requirement for ICC, tracheostomy, ICC dwell time, ventilator associated pneumonia	There were 3 times more conservative Mx failures (24% vs 8%) among conservative Mx for "prolonged mechanical ventilation" versus ventilation for a general anaesthetic only Authors concluded that the results suggest that occult PTX may be managed conservatively in haemodynamically stable patients undergoing mechanical ventilation just for an operation, although one third of those requiring a week or more of ICU care received ICC, and tension PTXs still occurred. Complications of pleural drainage remained unacceptably high.	(2 for progression to simple PTX, 5 for non-PTX related reasons). Mortality was 4 in each group. ICC complications occurred 11 times in ICC group (10 malpositioning). Incidence of pneumonia/empyema was 13 in observed group and 7 in ICC group. **Reason for ventilation:** 13 in conservative Mx group and 12 in the ICC group had ventilation for an operation only. 37 in conservative Mx group and 28 in ICC group had "prolonged ventilation".

				or adult respiratory distress syndrome) or global (death, ventilator days, ICU and hospital length of stay) Drainage complications		
Lee et al. 2010[16]	**Study Design:** Retrospective cohort study **Country:** Hong Kong **Site:** Prince of Wales Hospital, Shatin (university teaching hospital) **Time period:** Jan 2006 - Dec 2007	**Inclusion criteria:** Severely injured patients with blunt chest trauma undergoing thoracic CT found to have occult PTX **Age:** All ages **Insertion technique:** Not specified **Trauma type:** Blunt only **CT scanner:** Thoracic CT, unspecified model	**Total:** 44 occult PTX (36 patients) ICC group: 8 Conservative Mx group: 36 **Ventilated subgroup:** ICC group: 8 Conservative Mx group: 8	Nature and number of complications Mortality	Patients that received mechanical ventilation in the trauma room were more severely injured (ISS 48 vs 33) than those that received mechanical ventilation in the operating room. All those patients who were ventilated in trauma room received an ICC. No complications associated with conservative Mx. Since ICC is not without complication it may be possible to extend the concept	**Ventilated subgroup:** There were no complications or mortality in the conservative Mx group. In the ICC group there was 1 major complication (empyema) and 3 minor complications (persistent intercostal neuralgia and wound infection).

					of conservative Mx to those who received ventilation in trauma room within this study. **Occult PTX incidence:** 36.9% (44/119) significant blunt chest trauma undergoing CT scan.	
Llaquet Bayo et al. 2016[182]	**Study Design:** Retrospective cohort study **Country:** Spain **Site:** Single centre, Level 2 teaching hospital **Time period:** March 2006 - Dec 2013	**Inclusion criteria:** Polytrauma patients diagnosed with occult PTX and admitted to critical care section of hospital **Age:** Over 16 years **Insertion technique:** Not specified **Trauma type:** Blunt and penetrating **CT scanner:** Thoracic and abdominal, model not specified	**Total:** 126 occult PTX ICC group: 53 Conservative Mx group: 73 **Ventilated subgroup:** ICC group: 26 Conservative Mx group: 16	Success rate of conservative management (considered failed if ICC required) Tension PTX rate Hospital and ICU length of stay Mortality Drainage complications (poor positioning, loss, infection or bleeding	11% (8/73) failure of conservative Mx, 19% (3/16) in ventilated subgroup. 8 cases required ICC insertion: 5 for haemothorax, 3 for progression of PTX. 1 was prophylactical placed pre surgery. 3 patients presented complications associated with the drainage (2 inserted into subcutaneous tissue; 1 lost position).	**Ventilated subgroup:** In the conservative Mx group 3 patients required ICC placement (1 for progression of PTX, 2 for non-PTX related reasons). Mortality was 3 in conservative Mx group and 8 in ICC group. 2 complications of ICC in ventilated patients.

					Concluded that treatment of choice for occult PTX is conservative Mx including in mechanically ventilated patients. **Occult PTX incidence:** 11.6% (126/1087) polytrauma patients admitted to critical or semi-critical care sections of the hospital.	
Notrica et al. 2012[183]	**Study Design:** Prospective cohort study **Country:** USA **Site:** Multicentre, 16 institutions **Time period:** 2008-2009	**Inclusion criteria:** Patients with traumatic occult PTX **Age:** Under 18 years **Insertion technique:** Discretion of attending surgeon **Trauma type:** Blunt and penetrating	**Total:** 52 occult PTX (51 patients) ICC group: 3 Conservative Mx group: 49 **Ventilated subgroup:** ICC group: 1	Placement of ICC Hospital and ICU length of stay Ventilator days Indication for ICC Mortality Complications Average tidal volume and peak inspiratory pressure also measured	Only 2% (1/49) failed conservative Mx. 2 PTX progressed in size in conservative Mx group, only one required ICC. Authors concluded that this demonstrated safety of conservative Mx of occult PTX less than 16.5mm. The physical discomfort, potential morbidity and risk of	**Ventilated subgroup:** Neither group had progression of PTX nor need for ICC insertion. **Reason for ventilation:** 4 patients in conservative Mx group and 1 in ICC group underwent an operation.

		CT scanner: Unspecified site and model **Ventilation settings:** Average TV 7.2+/- 1.1ml/kg, average peak inspiratory pressure 19.7+/- 5.2mmHg	Conservative Mx group: 8		complications of ICC must now be compared to the relative safety of conservative Mx.	
Wilson et al. 2009[184]	**Study Design:** Retrospective cohort study **Country:** Canada **Site:** Multicentre, Used Nova Scotia Trauma Registry **Time period:** Oct 1994 - March 2003	**Inclusion criteria:** Blunt trauma patients with ISS >12 and PTX diagnosis (occult PTX was identified through review of imaging) **Age:** All ages **Insertion technique:** Not specified **Trauma type:** Blunt only **CT scanner:** Site or model not specified	**Total:** 68 occult PTX ICC group: 35 Conservative Mx group: 33 **Ventilated subgroup:** ICC group: 29 Conservative Mx group: 16	Hospital length of stay Mortality Intervention and time to intervention (ICC placement and its relation to mechanical ventilation)	There were no instances of PTX progression or tension PTX in the observation group. Length of stay was longer in ICC group (10 vs 7 days, p=0.01), mortality similar. Conclusion from authors: conservative Mx may be safe. **Occult PTX incidence:** 3.6% (68/1881) blunt trauma patients admitted.	**Ventilated subgroup:** No progression of PTX or tension PTX in either group. **Reason for ventilation:** In conservative Mx group, 16 patients had an operation. 10 of these received ventilation only for the operation.

Zhang et al. 2016[10]	**Study Design:** Retrospective cohort study **Country:** Singapore **Site:** Single centre, Tan Tock Seng Hospital **Time period:** Jan 2009 - Dec 2012	**Inclusion criteria:** Patients in trauma database with an CT scan visualising the thorax partially or fully showing occult PTX. **Age:** All ages **Insertion technique:** Not specified **Trauma type:** Blunt only **CT scanner:** 64 slice multidetector CT, any CT visualising the thorax	**Total:** 83 occult PTX ICC group: 35 Conservative Mx group: 48 **Ventilated subgroup:** ICC group: 7 Conservative Mx group: 5	Hospital length of stay Subsequent requirement for ICC Expanding PTX Wound infection Pleural effusion Empyema Mortality	Increased hospital length of stay for ICC group (13 days versus 5.5, p =0.008). No difference in mortality. 4/48 conservatively Mx patients had progression of PTX requiring ICC. ICC group 7/35 had complications and 3/35 had progression of PTX. ICC group were nearly 10 times more likely to have a complication (OR 9.92). Authors advocated for conservative Mx in light of inherent ICC complications. **Occult PTX Incidence:** 5.3% (83/1564) Ten Tock Seng Hospital trauma database.	**Ventilated subgroup:** In the conservative Mx group, 1 patient required ICC placement for progression of PTX.

PTX – pneumothorax; Mx – management; ICC – intercostal catheter; MV – mechanical ventilation; ICU – intensive care unit; CT – computed tomography; ISS – injury severity score; TV – tidal volume

3.3.3 Study design and interventions

The majority of the cohort studies (seven out of nine) were retrospective design.[10,16,167,169,170,182,184] The remaining two were prospective[181,183] and both included exclusively paediatric patients. Further details can be seen in Table 3.4. The intervention in all studies[10,16,63,65,167,169,170,179,181-184] was conservative management, which involved not inserting an ICC and monitoring clinically and/or radiographically for signs of progression of pneumothorax. Different terms were used throughout the different studies (e.g. observation, expectant management). The comparator group was ICC insertion. The insertion technique for the ICC was specified in all RCTs; two blunt dissection[63,179] and one blunt dissection or Seldinger technique.[65] In regards to cohort studies, three specified the technique: blunt dissection[170], 'at the operator's discretion'[183] and inserted by 'standard fashion'.[169] The insertion technique was unspecified in the remaining studies[10,16,167,181,182,184] (see Table 3.4).

3.4 Outcomes

This section describes the results of the primary and secondary outcomes. Where possible, meta-analysis was performed, and logistic regression, M-H and POR odds ratios and 95% confidence intervals have been displayed together to aid visual inspection.

Not all of the included studies provided data for every outcome predetermined by this review. A summary of the data that were available in the included studies can be found below (see Tables 3.5 and 3.6). Pain and analgesia requirements were not reported in any of the included trials or studies; all other outcomes were at least partially reported in the included studies. Full statistical analysis and figures (forest plots) of the sensitivity analyses of statistical models (see Section 2.3.5) that are referred to throughout this section, individual study odds ratios and group numbers are presented in Appendix 7 for reference. The trial by Enderson et al.[63] contributes a large amount of data in a number of outcomes, with a significantly higher incidence than the other RCTs. As a result, where possible, the influence of this study was tested through sensitivity analyses. The results of these are presented throughout this section, where applicable, and in Appendix 7.

Table 3.5: Summary of primary outcome data available in the included studies

	RCTs			Cohort studies								
Primary outcomes	Brasel et al.[179]	Enderson et al.[63]	Kirkpatrick et al.[65]	Ball et al.[170]	Collins et al.[169]	Fulton & Bratu[167]	Holmes et al.[181]	Lee et al.[16]	Llaquet Bayo et al.[182]	Notrica et al.[183]	Wilson et al.[184]	Zhang et al.[10]
Progression of PTX	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Yes	Yes	Partial	Partial
Tension PTX	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Yes	Yes	Yes	Yes
Incidence of pneumonia/empyema	No	No	Yes	No	Yes	Partial	No	Yes	Yes	No	No	Partial
ICC insertion (any reason)	No	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Yes	Yes	Partial	Partial

PTX – pneumothorax; ICC – intercostal catheter; Yes – data available for both groups; No – no data available (shaded area); Partial – data available in conservative management group only (diagonal line shading)

Table 3. 6 : Summary of secondary outcome data available in the included studies

	RCTs			Cohort studies								
Secondary outcomes	Brasel et al.[179]	Enderson et al.[63]	Kirkpatrick et al.[65]	Ball et al.[170]	Collins et al.[169]	Fulton & Bratu[167]	Holmes et al.[181]	Lee et al.[16]	Llaquet Bayo et al.[182]	Notrica et al.[183]	Wilson et al.[184]	Zhang et al.[10]
ICC insertion (tension PTX)	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Yes	Yes	Yes	Yes
ICC insertion (progression to simple PTX)	Yes	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Yes	Yes	Partial	Partial
ICC insertion (non-PTX reason)	No	Yes	Yes	Yes	Yes	Partial	Yes	Yes	Yes	Yes	Partial	Partial
Mortality	No	No	Yes	No	Yes	Partial	No	Yes	Yes	No	No	No
Haemodynamic instability	No	No	No	No	No	No	No	No	Yes	No	No	No
ICC complications	Yes	Partial	Yes	Yes	Yes	Partial	No	Yes	Yes	No	No	Yes
ICU LoS	No	No	Yes	No	Yes	Partial	No	No	Yes	No	No	No
Hospital LoS	No	No	Yes	No	Yes	Partial	No	No	Yes	No	No	No
MV duration	Yes	No	Yes	No	No	Partial	Yes	No	No	No	No	No
Duration of ICC dwelling	No	No	Yes	No	Yes	No	No	No	No	No	No	No
Pain and analgesia requirement	No	No	No	No	No	No	No	No	No	No	No	No

PTX – pneumothorax; LoS – length of stay; ICC – intercostal catheter; MV – mechanical ventilation; ICU – intensive care unit; Yes – data available for both groups; No – no data available (shaded area); Partial – data available in conservative management group only (diagonal line shading)

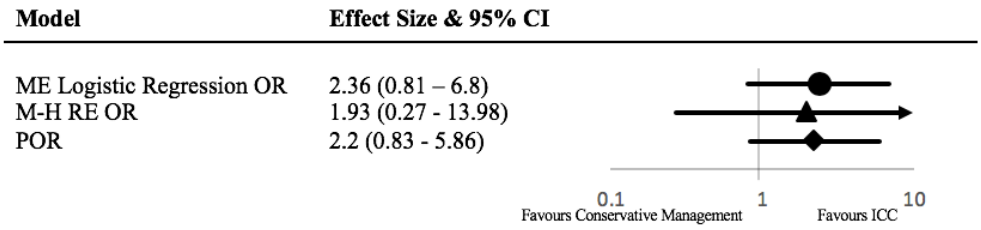
Legend (for table 3.5 and 3.6)

	No data available
	Data available in conservative Mx group only

3.4.1 Primary outcomes

3.4.1.1 Progression of pneumothorax

Incidence of progression of pneumothorax was reported in all included studies for the conservative management group (see Table 3.5). Three cohort studies[10,167,184] did not report progression of pneumothorax in the ICC ventilated patient group (see Table 3.5). The rate of progression of pneumothorax within the RCTs in the conservative management group was 15.1% (14 out of 93) compared with 9.8% (six out of 61) in the ICC group. Enderson et al.[63] reported eight cases in the conservative management group, making up more than half (eight out of 14) of the reported cases. Meta-analysis using a mixed-methods logistic regression model showed no statistical difference between the groups, but suggested that patients managed with initial ICC insertion had 2.36 times decreased odds of pneumothorax progression (95% CI 0.81-6.8; see Figure 3.2). Similar relative effects were found from the sensitivity analyses with other statistical models (see Figure 3.2, Appendix 7: Figures 7.1 and 7.2). Sensitivity analyses performed to explore the influence of the study by Enderson et al.[63] showed a logistic regression odds ratio of 0.85 (95% CI 0.25-2.94) and a M-H odds ratio of 0.86 (95% CI 0.25-2.99, see Appendix 7: Figure 7.3). In both analyses, the effect estimate changed in favour of conservative management, and a reduced relative difference between groups, with 15% decreased odds.



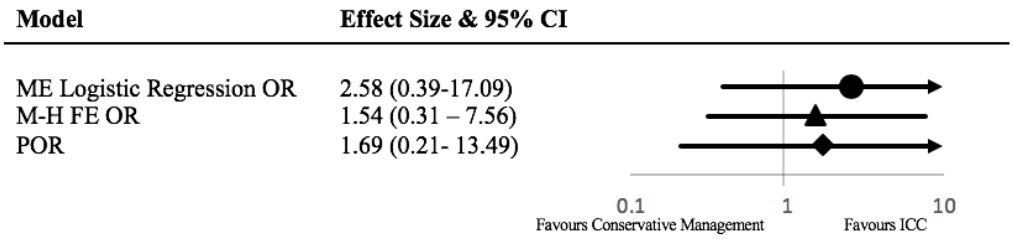
Principal analysis of three RCTs using mixed effect logistic regression. Other analyses presented are available in Appendix 7 (see Figures 7.1 and 7.2).

CI – confidence interval, ME – mixed effects, M-H – Mantel-Haenszel, RE – random effects, POR – Peto odds ratio, OR – odds ratio

Figure 3.2: Progression of pneumothorax – randomised controlled trials

In the cohort studies, there were three out of 66 (4.5%) in the conservative management group and two out of 55 (3.6%) in the ICC group. The meta-analysis for cohort studies showed similar results to those of the RCTs (logistic regression odds ratio = 2.58, 95% CI 0.39-17.09), albeit with less precision (wider confidence

intervals) and greater disparity between the different statistical models in the sensitivity analyses (see Figure 3.3, Appendix 7: Figures 7.4 and 7.5).



Principal analysis of six cohort studies using mixed effect logistic regression. Other analyses presented are available in Appendix 7 (see Figures 7.4 and 7.5).

CI – confidence interval, ME – mixed effects, M-H – Mantel-Haenszel, FE – fixed effects, POR – Peto odds ratio, OR – odds ratio

Figure 3.3: Progression of pneumothorax – cohort studies

3.4.1.2 Intercostal catheter insertion (any reason)

ICC insertion (for any reason) was reported in all but one study[179] in the ventilated conservative management group. In the ventilated ICC group, four studies[10,167,179,184] did not report the incidence of ICC insertion (for any reason) (see Table 3.5). A breakdown of the reasons for ICC insertion is presented in Table 3.7. Further description and analysis of the ICC insertion reasons are presented in Sections 3.4.2.2 to 3.4.2.4.

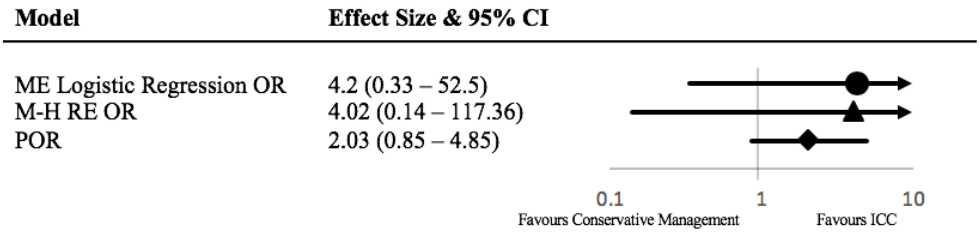
Table 3.7: Breakdown of intercostal catheter insertion reasons

ICC insertion reason	Conservative Mx group	ICC group
Any reason	24/150 (16%)	13/107 (12.1%)
Tension PTX	4/159 (2.5%)	1/116 (0.8%)
Progression to simple PTX	13/159 (8.2%)	3/116 (2.5%)
Progression of PTX (i.e. simple + tension)	17/159 (10.6%)	4/116 (3.4%)
Non-PTX reason	9/150 (6%)	9/107 (8.4%)

ICC – intercostal catheter; Mx – management; PTX – pneumothorax

In the RCTs, there were 18 out of 84 (21.4%) in the conservative management group and in the ICC group there were eight out of 52 (15.4%). Meta-analysis showed that the ICC group had 4.2 times decreased odds of having an ICC inserted (95% CI 0.33-52.5). There is however low certainty in these findings due to noticeable

imprecision evidenced by the large range of confidence intervals in the logistic regression model and in the M-H sensitivity analysis (see Figure 3.4, Appendix 7: Figures 7.6 and 7.7). The effect size is also skewed by Enderson et al.[63] due to the high incidence of ICC insertion in the conservative management group. Removing Enderson et al.[63] to assess its affect leaves data from one RCT[65], with a calculated odds ratio of 1.00 (95% CI 0.35-2.8).

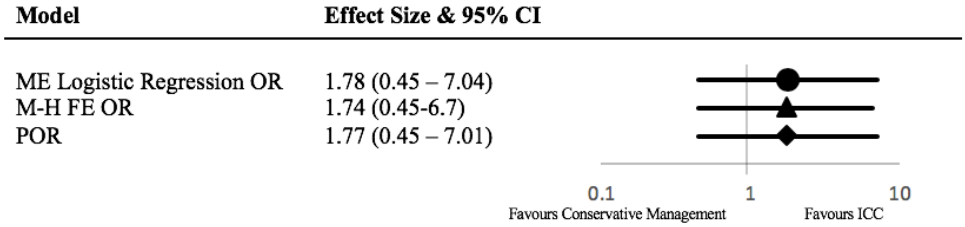


Principal analysis of two randomised controlled trials using mixed effect logistic regression. Other analyses presented are available in Appendix 7 (see Figures 7.6 and 7.7).

CI – confidence interval, ME – mixed effects, M-H – Mantel-Haenszel, RE – random effects, POR – Peto odds ratio, OR – odds ratio

Figure 3.4: Intercostal catheter insertion (any reason) – randomised controlled trials

In the cohort studies, there were six out of 66 (9.1%) in the conservative management group with the same rate (9.1%, five out of 55) in the ICC group. Meta-analytical modelling showed different results to the RCTs, although this was very consistent across the three models used, with an odds ratio of 1.78 (95% CI 0.45 – 7.04). This was also shown also in the sensitivity analyses (see Figure 3.5, Appendix 7: Figures 7.8 and 7.9).



Principal analysis of six cohort studies using mixed effect logistic regression. Other analyses presented are available in Appendix 7 (see Figures 7.8 and 7.9).

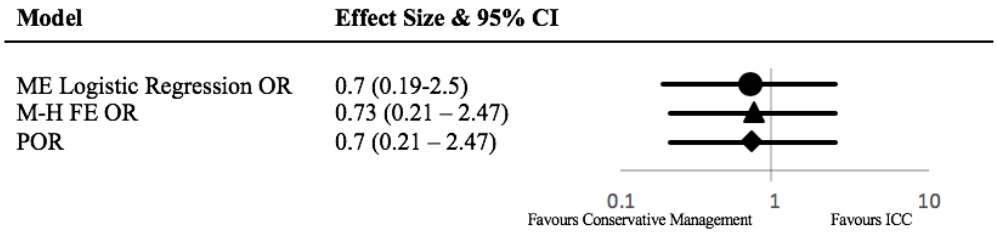
CI – confidence interval, ME – mixed effects, M-H – Mantel-Haenszel, FE – fixed effects, POR – Peto odds ratio, OR – odds ratio

Figure 3.5: Intercostal catheter insertion (any reason) – cohort studies

3.4.1.3 Incidence of pneumonia/empyema

Data for incidence of pneumonia/empyema were available from one RCT[65], with calculated odds ratio suggested a non-significant 66% decreased chance of developing pneumonia/empyema (OR 1.66, 95% CI 0.59 – 4.65) for the ICC group.

In contrast to the results for RCTs presented in Figure 3.6, meta-analysis of cohort studies showed a decreased odds ratio for the incidence of pneumonia and empyema for the conservative management group (odds ratio = 0.7, 95%CI 0.19 – 2.5; see Figure 3.7). Sensitivity analyses showed similar results (see Figure 3.6, Appendix 7: Figures 7.10 and 7.11).



Principal analysis of three cohort studies using mixed effect logistic regression. Other analyses presented are available in Appendix 7 (see Figures 7.10 and 7.11).

CI – confidence interval, ME – mixed effects, M-H – Mantel-Haenszel, FE – fixed effects, POR – Peto odds ratio, OR – odds ratio

Figure 3.6: Pneumonia/empyema incidence – cohort studies

3.4.1.4 Incidence of tension pneumothorax

The incidence of tension pneumothorax was low in both the conservative management and ICC groups. Four instances were reported (four out of 159; 2.5%) in the conservative management group, all in the RCTs.[63,65] Enderson et al.[63] reported the highest incidence, with three cases in their conservative management group. There was one incidence in 152 cases (0.7%) reported in the ICC group, which was reported in a cohort study.[182]

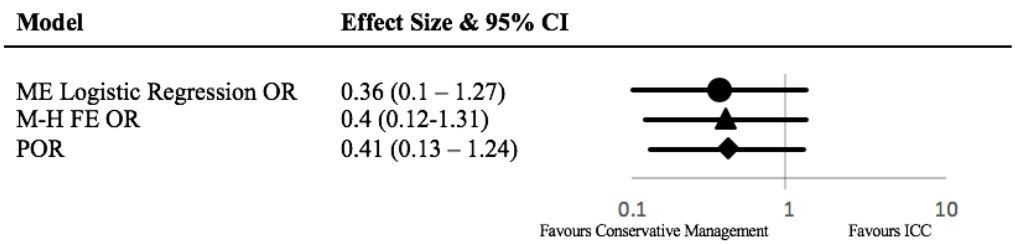
3.4.2 Secondary outcomes

3.4.2.1 Mortality (all-cause)

One experimental study[65] reported data for mortality. Four patients in each group died. Calculation of the odds ratio for this study confirmed a non-statistically

significant decrease in mortality in the conservative management group (odds ratio 0.78, 95% CI 0.18-3.34).

Across the included cohort studies, there was a higher observed incidence (12 out of 40) of mortality in the ICC group compared to the conservative management group (four out of 50). Logistic regression produced an odds ratio of 0.36 (95% CI 0.1-1.27) confirmed by analyses using alternative methods (see Figure 3.7, Appendix 7: Figures 7.12 and 7.13).



Principal analysis of three cohort studies using mixed effect logistic regression. Other analyses presented are available in Appendix 7 (see Figures 7.12 and 7.13)

CI – confidence interval, ME – mixed effects, M-H – Mantel-Haenszel, FE – fixed effects, POR – Peto odds ratio, OR – odds ratio

Figure 3.7: Mortality (all-cause) – cohort studies

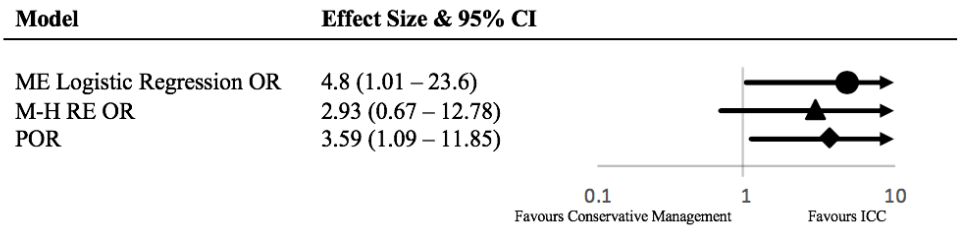
3.4.2.2 Intercostal catheter insertion (tension pneumothorax)

All five tension pneumothoraces recorded in the included studies required ICC insertion (see Section 3.4.1.3). There were four in the conservative management group and one in the ICC group.

3.4.2.3 Intercostal catheter insertion (progression to simple pneumothorax)

A statistically significant difference was seen in the logistic regression analysis with patients in the ICC group having 4.8 times less chance of receiving an ICC for progression to a simple pneumothorax (95% CI 1.01 – 23.6). Calculated effect estimates from sensitivity analyses with other statistical models varied (see Figure 3.8, Appendix 7: Figures 7.14 and 7.15), likely due to the number of zero events and use of continuity correction in the M-H model in the ICC group in two of the RCTs.[63,179] Sensitivity analyses performed exploring the effect of the study by Enderson et al.[63] showed a decreased odds ratio and loss of statistical significance, however this was still in favour of the ICC group (logistic regression odds ratio 2.25,

95% CI 0.4 – 12.3 and a M-H odds ratio of 1.83, 95%CI 0.37 – 9.02) (see Appendix 7: Figure 7.16).

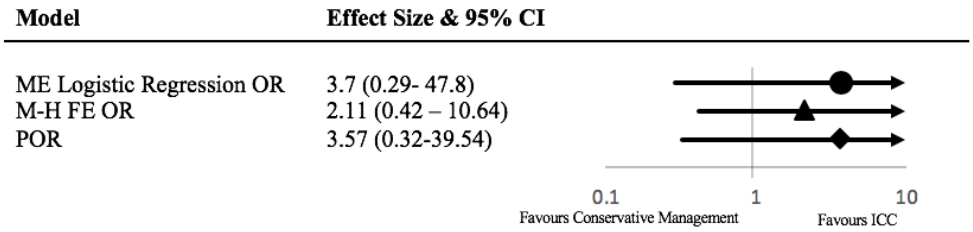


Principal analysis of three RCTs using mixed effect logistic regression. Other analyses presented are available in Appendix 7 (see Figures 7.14 and 7.15).

CI – confidence interval, ME – mixed effects, M-H – Mantel-Haenszel, RE – random effects, POR – Peto odds ratio, OR – odds ratio

Figure 3.8: Intercostal catheter insertion (progression to simple pneumothorax) – randomised controlled trials

Meta-analyses of the cohort studies revealed similar results to those of the RCTs, with 3.7 times decreased odds of receiving an ICC for progression to a simple pneumothorax (95% CI 0.29 – 47.8). The effect was not statistically significant and showed greater imprecision than the analysis of experimental studies (see Figure 3.9). The use of continuity correction in the M-H model is again seen to have an effect in reducing the effect estimate compared to the other statistical models (see Figure 3.9, Appendix 7: Figures 7.17 and 7.18).



Principal analysis of six cohort studies using mixed effect logistic regression. Other analyses presented are available in Appendix 7 (see Figures 7.17 and 7.18).

CI – confidence interval, ME – mixed effects, M-H – Mantel-Haenszel, FE – fixed effects, POR – Peto odds ratio, OR – odds ratio

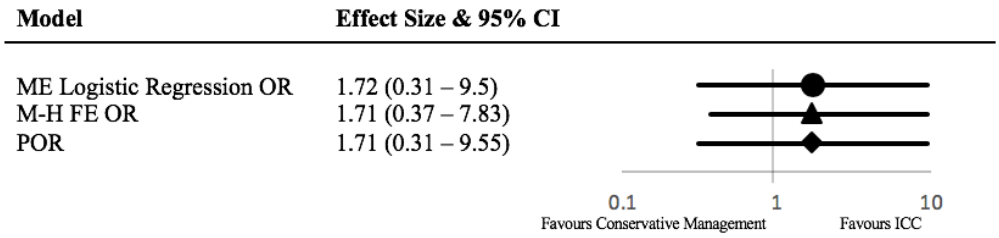
Figure 3.9: Intercostal catheter insertion (progression to simple pneumothorax) – cohort studies

3.4.2.4 Intercostal catheter insertion (non-pneumothorax reason)

Meta-analysis using logistic regression suggests a 23% decreased chance of receiving an ICC for non-pneumothorax reasons in the conservative management

group (OR 0.77, 95% CI 0.2 – 2.6). Due to double arm zero event results in one study[63], two stage meta-analytical models (M-H/Peto) could not be utilised. Therefore, sensitivity analyses with these models were not undertaken for the RCTs for this outcome.

Logistic regression for the cohort studies suggested increased odds of receiving an ICC for non-pneumothorax reasons in the conservative management group, with an odds ratio of 1.72 (95% CI 0.31 – 9.5; see Figure 3.11). This was again replicated in the sensitivity analyses (see Figure 3.10, Appendix 7: Figures 7.19 and 7.20). However, the incidence was lower in the conservative management group (3.5% versus 5.5%). The disparity between the analyses and incidence is likely due to three studies[10,167,184] that were not included in the meta-analysis as they only had data for the conservative management group. In these three studies[10,167,184], there was no reported incidence of ICC insertion for non-pneumothorax reasons.



Principal analysis of six cohort studies using mixed effect logistic regression. Other analyses presented are available in Appendix 7 (see Figures 7.19 and 7.20).

CI – confidence interval, ME – mixed effects, M-H – Mantel-Haenszel, FE – fixed effects, POR – Peto odds ratio, OR – odds ratio

Figure 3.10: Intercostal catheter insertion (non-pneumothorax reason) – cohort studies

3.4.2.5 Hospital length of stay

One RCT[65] reported the following hospital length of stay (median and interquartile range [IQR]): 18.0 days (10.0-47.0) for the conservative management group, and 16.0 days (8.5-42.0) for the ICC group. Three cohort studies[167,169,182] reported on this outcome; results are displayed in Table 3.8. Hospital length of stay was reduced in the conservative management group.

Table 3.8: Hospital length of stay reported in three included cohort studies

Study	Conservative management group	Intercostal catheter group
Collins et al.[169]	13 (1-32) days Mean (range)	18.8 (6-36) days Mean (range)
Fulton & Bratu[167]	17.8 (3-79) days Mean (range)	
Llaquet Bayo et al.[182]	17.2 (8.3-27.9) days Median (IQR)	19.5 (6.4-28.4) days Median (IQR)

IQR - interquartile range

3.4.2.6 Intensive care unit length of stay

One RCT[65] reported the following ICU length of stay (median and IQR): 5.0 (2.0-11.5) days for the conservative management group, and 4.0 (1.0-9.5) days for the ICC group. The outcomes from three cohort studies[167,169,182] are displayed in Table 3.9. The data from the cohort studies suggest that the conservative management group had a shorter ICU length of stay, and the difference between groups appeared more pronounced than the difference in hospital length of stay (see Table 3.8).

Table 3.9: ICU length of stay reported in three included cohort studies

Study	Conservative management group	Intercostal catheter group
Collins et al.[169]	4.14 (0-12) days Mean (range)	13.6 (2-30) days Mean (range)
Fulton & Bratu[167]	4.4 (1-14) days Mean (range)	
Llaquet Bayo et al.[182]	8.4 (7-20.3) days Median (IQR)	16.1 (6.7-22.8) days Median (IQR)

IQR - interquartile range

3.4.2.7 Duration of mechanical ventilation

Duration of mechanical ventilation was recorded in two RCTs[65,179] and two cohort studies.[167,181] RCT results are displayed in Table 3.10. There were minimal differences between the two groups. The cohort studies were both paediatric studies

and only reported mechanical ventilation duration in the conservative management group. Fulton & Bratu[167] had a mean of 2.3 days and range of 0 to 13. Holmes et al.[181] had two patients; one received mechanical ventilation for two hours and the second patient for 16 days.

Table 3.10: Mechanical ventilation duration reported in two included randomised controlled trials

Study	Conservative management group	Intercostal catheter group
Brasel et al.[179]	1 (1-19) days Median (range)	2 (1-4) days Median (range)
Kirkpatrick et al.[65]	3.0 (0-8.0) days Median (IQR)	2.5 (0-6.5) days Median (IQR)

IQR - interquartile range

3.4.2.8 Duration of intercostal catheter dwelling

Duration of ICC dwelling was recorded in one RCT[65] and one cohort study.[169] This was only reported in the ICC group. Kirkpatrick et al.[65] reported a median and interquartile range of 5.0 (4.0-8.0) days. Collins et al.[169] had a mean and range of 6.33 (2-20) days and a median of three days.

3.4.2.9 Haemodynamic instability

None of the RCTs reported data on haemodynamic instability. One cohort study[182] reported on haemodynamic instability, which was defined as systolic blood pressure less than 90mmHg or heart rate greater than 100 beats per minute. Haemodynamic instability was reported in nine out of 16 (56%) patients in the conservative management group and 14 out of 26 (54%) patients in the ICC group; there was no difference between the two groups.

3.4.2.10 Pain and analgesia requirements

None of the included studies reported any data on pain or analgesia requirements.

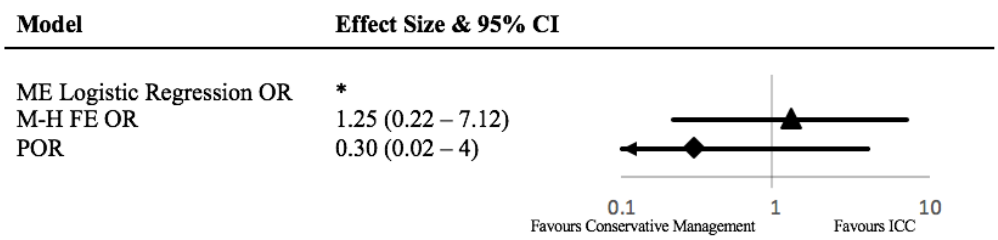
3.4.3 Intercostal catheter complications

ICC complications were reported in the majority of studies[10,16,63,65,169,170,179,182] (8/12). The overall rate of ICC complication in both groups was 21% (31 out of 147).

3.4.3.1 Intercostal catheter complication (composite)

In the RCTs, there were 11 out of 49 (22%) ICC complications in the ICC group, and one out of 20 (5%) in the conservative management group when an ICC was required to be inserted. Meta-analysis for this outcome using logistic regression or M-H models could not be performed. The logistic regression model could not be performed due to no events being reported in the conservative management group and the M-H model could not be performed due to double arm zero event in one study.[179] Data from Kirkpatrick et al.[65] gives a calculated M-H odds ratio of 0.12 (95% CI 0.01 – 2.26), which was not statistically significant.

In the analysis of cohort studies, the continuity correction used in the M-H model had a marked effect on the calculated effect estimate (see Figure 3.11, Appendix 7: Figures 7.21 and 7.22). This is likely due to the small numbers of patients (six) in the conservative management group requiring placement of an ICC and no complications occurring in this group. A total of 11 complications out of 60 ICCs placed (18.3%) were reported in the ICC groups in the included cohort studies.



Principal analysis of five cohort studies using mixed effect logistic regression. Other analyses presented are available in Appendix 7 (see Figures 7.21 and 7.22).

CI – confidence interval, ME – mixed effects, M-H – Mantel-Haenszel, FE – fixed effects, POR – Peto odds ratio, OR – odds ratio

** due to zero events in all studies in conservative management group, a logistic regression model could not be used*

Figure 3.11: Intercostal catheter complications – cohort studies

3.4.3.2 Intercostal catheter complication (breakdown)

ICC complications were divided into malpositioning, infection, organ injury and vascular injury. A summary of the breakdown is presented in Table 3.11 and a further description follows below.

Table 3.11: Intercostal catheter Complications Breakdown for All Included Studies

	Conservative management group *(26 ICC inserted and complications documented)*	**Intercostal catheter group** *(109 had complications documented)*
Composite	1 (3.8%)	22 (20%)
Malpositioning	0	13 (10.7%)
Infection	1 (3.8%)	3 (2.8%)
Organ injury	0	0
Vascular injury	0	2 (1.6%)
Other/unspecified	0	4 (3.3%) *

**Other/unspecified*

- Collins et al.[169]: patient self- removed intercostal catheter, requiring replacement

- Kilpatrick et al.[65]: patient self-removed intercostal catheter, requiring replacement

- Lee et al.[16]: persistent intercostal neuralgia

- Zhang et al.[10]: unspecified

Kirkpatrick et al.[65] reported ten malpositioning complications, all in the ICC group, with eight of these requiring replacement ICCs. In the cohort studies, there were three malpositioning complications, two in Llaquet Bayo et al.[182] and one in Ball et al.[170], with all three requiring replacement ICCs.

Enderson et al.[63] reported one infective complication in the conservative management group, where a patient who required an ICC placement for progression of pneumothorax developed an empyema.

Lee et al.[16] reported three infective complications in the ICC group. One patient developed an empyema and two patients developed a local wound infection. In this study, it was not possible to compare ICC management against conservative management as there were no requirements for ICC placement in the conservative management group.

There were two vascular injuries in the included studies, both reported in Ball et al.[170] in the ICC group. There were no organ injuries reported in any of the included studies.

Chapter 4: Discussion

This chapter discusses the results of the systematic review presented in the previous chapter, its limitations, and the implications for practice and future research.

4.1 Results in context

Conservative management can be considered a safe alternative to ICC insertion for the initial management of occult pneumothoraces in mechanically ventilated patients. The results of the systematic review of available evidence presented in this thesis show that conservative management and ICC insertion are both equally effective. Considering the nature of the evidence and results presented, including the small sample size included and imprecision in many of the results reported, this remains an uncertain result. Despite this, given the non-invasive nature of conservative management, the low incidence of tension pneumothorax and the highly monitored environment in which mechanically ventilated patients are cared for, the evidence suggests conservative management may be favoured over ICC insertion, considering the evident harms associated with ICC insertion.

Considering the effectiveness of the two management strategies, ICC insertion for progression to simple pneumothorax was the only outcome that showed a benefit for ICC insertion. Despite relatively equal effectiveness being shown in the other measures, the evidence did suggest the risk was reduced in the ICC group for progression of pneumothorax, ICC insertion for any reason and incidence of pneumonia/empyema. However, the risk of mortality and ICC insertion for non-pneumothorax reason was reduced in the conservative management group. Interestingly, there was a higher risk of receiving an ICC for progression of pneumothorax in the conservative management group despite no difference being shown in the outcome of progression of pneumothorax. This is likely due to a proportion of the pneumothoraces that progressed in the ICC group having been managed without the insertion of another ICC. The pneumothoraces, in some cases, could be resolved by placing the ICC on suction (see Section 1.4.2).

The outcomes of progression of pneumothorax, ICC insertion for any reason and ICC insertion for progression to simple pneumothorax in the RCT analysis were heavily skewed in favour of the ICC group by the study by Enderson et al.[63], which had a much higher incidence of progression of pneumothorax than the other two RCTs.[65,179] The reason for this higher incidence is unclear from the information provided, however it can be speculated that the common ventilator settings of the time may have contributed to it (see Section 1.5.2). Prior to the ARDSnet (Acute Respiratory Distress Syndrome Network) article[122] published in 2000, it was common for tidal volumes to be set at 10-12ml/kg. Since this study was conducted, it has been recognised that there are better outcomes in all patient groups when lower tidal volumes are used[126,127], with 6-8ml/kg ideal body weight now routinely being used.[124,125] The use of these lower tidal volumes requires lower pressures to be applied to the lungs by the ventilator and as the pressure gradient is what is believed to cause progression of pneumothorax and development of tension pneumothoraces; lower pressures will likely lead to a lower incidence of both (see Section 1.2.1). Unfortunately, tidal volumes were not reported in the study by Enderson et al..[63] Sensitivity analyses performed to explore the influence of the study by Enderson et al.[63] suggested that the risk of progression of pneumothorax was lower in the conservative management group, and ICC insertion for progression to simple pneumothorax lost statistical significance.

The length of time that a patient is ventilated may also increase the risk of progression of pneumothorax, however most studies did not investigate this link. Through subgroup analysis, Kirkpatrick et al.[65] found that there was a trend toward a higher incidence of progression of pneumothorax when patients required sustained mechanical ventilation; the risk increased threefold after seven days.

For some outcomes, there were noticeable differences between effect estimates from RCTs and cohort studies; these included contradictory results in the incidence of pneumonia/empyema, and significant decreased risk of mortality and decreased length of stay in both hospital and ICU in the conservative management group in the cohort studies. This may be due to differences in how confounding factors were handled between study designs. It is unclear what the exact confounding factors were, however it is likely that in the cohort studies, more severely injured patients

would be preferentially chosen to receive an ICC if they had an occult pneumothorax. This would then explain the higher mortality, higher incidence of pneumonia/empyema and longer time in both ICU and hospital for the ICC group in the cohort studies. The only objective evidence to support the acuity of included patients was the injury severity score (ISS), however there was no significant difference in the baseline characteristics of the cohort studies (see Table 3.3).

In regards to the safety of the two management strategies, the major concerns with conservative management are progression of pneumothorax, tension pneumothorax and need for ICC insertion. The incidence of progression of pneumothorax was 15.1% in RCTs and 4.5% in cohort studies. The incidence of tension pneumothorax in this series was 2.5%, with three out of the four reported in one RCT.[63] If we disregard this study, the incidence becomes 0.7%. There was also a tension pneumothorax reported in the ICC group. It occurred in ICU 48 hours after the initial ICC was inserted and required another ICC to be inserted.[182] It is important to note that the insertion of an ICC does not completely negate the risk of tension pneumothorax. Investigating the requirement for an ICC insertion for any reason in the conservative management group in this research showed almost 80% of patients in the RCTs did not require the invasive procedure of an ICC insertion. As this procedure is invasive, it comes with a set of risks and potential complications, including malpositioning (and failure of drainage), infection and damage to internal structures (see Section 1.4.3). This is the safety concern with ICC insertion. The total incidence of ICC complications in this series was 17% (20% in the ICC group), in keeping with previously published literature, with a reported incidence of 20-35%.[66,85-89] The incidence was significantly higher in the ICC group; possible explanations for this include suboptimal conditions in urgent ICC insertion and easier insertion following pneumothorax progression. ICCs placed initially in trauma patients are often inserted in suboptimal conditions due to reduced access to the patient, with other procedures occurring and less attention paid to ensuring adequate sterile conditions and optimal positioning due to time pressure. When an ICC is inserted for progression of pneumothorax or haemothorax in patients managed with conservative management, there is often time to ensure optimal conditions and positioning are used (except in the case of a tension pneumothorax).

In the case of insertion of an ICC for pneumothorax, it will be easy after it has progressed as there will be more space within the pleural cavity. This should make placement of a large-bore ICC easier and will also allow for insertion of a pigtail drain via the Seldinger technique.

Pigtail drains are becoming popular as it is a less invasive procedure than the blunt dissection technique required for a large-bore ICC (see Section 1.4.1.3). A RCT[78] reported significantly lower pain scores in patients who received a pigtail drain versus a large-bore ICC on the day of insertion and over the days after insertion. The same author also investigated the effectiveness of pigtail catheters for drainage of pneumothoraces, with comparable efficacy to wide bore ICCs.[185] A meta-analysis[186] investigating pigtail catheters for all causes of pneumothoraces showed a similar management success rate and a lower complication rate, however within the traumatic subgroup, both the success rate and complication rate were the same for each technique. Similar findings were found in a meta-analysis[187] investigating the use of pigtail catheters for management of traumatic pneumothoraces and haemothoraces, with a success rate of 90-100%. Unfortunately, none of the studies in this series reported which method was used for insertion of ICCs in the conservative management group. However, it would be interesting to ascertain whether the use of a pigtail catheters for progression of pneumothorax improves outcomes.

Compared to the previous 'mini-reviews'[1,2], this review had a higher number of patients within the RCTs and cohort studies, and a higher number of outcomes were investigated. This provides a more complete picture of the benefits, harms and adverse effects of both management strategies. The results of this review are in keeping with the findings of previous 'mini-reviews', however the more explicit methods used, and the larger evidence pool increase the certainty in the findings. Nevertheless, there remains the need for further large multi-centre RCTs to fully address this question as the evidence is still limited in this review. The full analysis of the OPTICC study[168] will add additional information to this query.

Overall, from the limited evidence found in this systematic review, conservative management and ICC insertion was shown to be equally effective for the management of occult pneumothoraces in mechanically ventilated patients.

Conservative management can be considered a safe method of managing occult pneumothoraces in mechanically ventilated patients, with the caveat that patients are in a highly monitored environment, caregivers are aware the patient has an occult pneumothorax and there is appropriate staff readily available to recognise and treat a tension pneumothorax. The lower rate of ICC complications in the 20% of patients that required a subsequent ICC insertion further adds to this safety.

4.2 Limitations of included studies

The limitations of the studies identified and included in this systematic review appear to fall under three main categories: rare events, small studies and inability to find/access raw data.

The majority of predefined outcomes presented in this systematic review had low incidence; this was especially the case in observational studies. Due to the low incidence and often small study size, there was a high proportion of zero event arms in the included studies. Some studies had double arm zero events (i.e. no events recorded in either group). This made meta-analysis difficult (see Section 2.3.5) and, in some outcomes, conducting a meta-analysis was not feasible at all. Despite single and double arm zero event studies not always being able to be included in meta-analysis, they did add weight to the rarity of some outcomes in this systematic review and provided additional important data to help ascertain the safety of the two management strategies.

Unfortunately, there is likely to be available data that were not included in this systematic review due to the inability to access it. All but two[65,167] of the included studies had ventilated patients as a subset of the total study and they often did not report the outcomes for ventilated patients separately, hence these data were lost to this systematic review. Some data were clarified with the authors, however many of the studies were from more than ten years ago and the data are no longer available, and some authors did not respond to correspondence. In addition, two cohort studies[10,184] did not report most of the data for the ICC group, especially for the ventilated subgroup. Due to this, data from these two studies could not be included in any meta-analyses.

4.3 Limitations of systematic review

The limitations inherent to this systematic review include small sample sizes, sparse data and parts of the review being completed by a single reviewer only. Due to the small sample size in the RCTs available on this topic and observational data being essential to gaining a picture of adverse events, an *a priori* decision was made to include cohort studies (prospective and retrospective).[146] In addition to the small sample size, there was sparsity of data, which led to high imprecision (wide confidence intervals) for the majority of outcomes. Due to this, there is a low certainty of the findings from this review.

The screening process was, in most parts, performed by one reviewer. The screening of titles, abstracts and full texts was performed by a single reviewer, except in the case where it was deemed unclear whether an article should be included or not. The use of a single reviewer may have resulted in overlooking and missing relevant articles. To minimise this, the title and abstracts were screened twice, and a hand search of the included study reference lists occurred. Data extraction was also performed by a single reviewer which may have led to data handling errors. Care was taken to ensure accurate data extraction and data were crossed checked with the articles, once extracted.

4.4 Implications for practice

The main implications of the results of this systematic review are that the best available evidence suggests that conservative management can be considered a safe management strategy for occult pneumothoraces in mechanically ventilated patients, and that ICC complications are common. When conservative management was used in the RCTs in this series, nearly 80% of patients did not require an ICC to be inserted for any reason, meaning four out of five patients were successfully managed without the need for an invasive procedure. When an invasive procedure was required, almost one in five patients had an ICC complication, with many of these requiring insertion of another ICC. Importantly, inserting an ICC did not necessarily stop a pneumothorax from progressing and a tension pneumothorax could still have occurred.

4.5 Implications for future research

Two of the included RCTs[65,179] used respiratory distress as their primary outcome. This was not included as an outcome in this systematic review due to the subjective nature of respiratory distress, the lack of definition from one RCT[179] and a long list of possibilities from the second[65], many of which could have been confounded by other factors. Consistent use of the same, important, objective outcomes would have aided interpretation and synthesis. This could be aided by the use of a core set of outcomes through the COMET (Core Outcome Measures in Effectiveness Trials) initiative, which aims to develop and encourage application of an agreed standardised set of outcomes to be reported in clinical trials.[188] There is currently no core outcome set for investigating the management of pneumothoraces.[189]

There is scope to include patient centred outcomes, such as pain, in future RCTs, using validated tools for measuring pain in mechanically ventilated and sedated patients[151,152] or by the surrogate of analgesia requirements. Both pain and opiate use has been shown to be a risk factor for ICU delirium, especially in the older population, which can increase duration of ventilation and ICU length of stay.[190,191]

A related focus that could be of interest would be to investigate the use of the Seldinger technique pigtail drain versus a larger bore ICC for patients managed conservatively that require an ICC insertion for progression of pneumothorax. Pigtail drains have been shown to produce less pain than a larger bore ICC[78] and they leave a smaller scar. If pigtail drains are shown to be non-inferior, they could be used more readily in this situation.

4.6 Conclusions

More evidence is required to fully inform the effectiveness of conservative management for occult pneumothoraces in mechanically ventilated patients. However, the evidence we have to date suggests that conservative management is a safe method for the management of occult pneumothoraces in mechanically ventilated patients, provided that the patients are in a highly monitored environment, the caregivers are aware that the patient has an occult pneumothorax and that there is appropriate staff available to recognise and treat tension pneumothorax if it occurs. To promote consistency in practice, clear guidelines should be created, aligning

which patients can be conservatively managed and how progression of pneumothorax is to be monitored.

Appendices

Appendix 1: Systematic review protocol

Wolters Kluwer permits use of the final peer-reviewed manuscript of this Protocol in print thesis.

Effectiveness and Safety of Conservative Management for Occult Pneumothorax in Mechanically Ventilated Patients: A Systematic Review Protocol

Authors

Jeremy A Smith [1, 2] Paul Secombe[3] Edoardo Aromataris[1]

1. Joanna Briggs Institute, Faculty of Health and Medical Sciences, The University of Adelaide, SA 5005.

2. Intensive Care Unit, St Vincent's Hospital, Melbourne, VIC 3065

3. Intensive Care Unit, Alice Springs Hospital, Alice Springs NT 0870

Abstract

Objective: This systematic review aims to synthesise available evidence investigating the effectiveness and safety of conservative management for occult pneumothorax in mechanically ventilated patients.

Introduction: Occult pneumothorax is air within the pleural cavity that is diagnosed on a CT scan but was not suspected on the basis of preceding clinical examination or supine chest x-ray. Its incidence has increased with the increased use of CT scans for trauma. Currently, there is no consensus on how to manage these, especially in patients requiring mechanical ventilation. Common practice is to place a prophylactic intercostal catheter (ICC) to stop the potential development of a tension pneumothorax, this however brings with it a 20% risk of major complications from the ICC insertion. Recent evidence may suggest that occult pneumothorax in mechanically ventilated patients can be managed with conservatively, rather than using a prophylactic ICC as first-line management.

Inclusion Criteria: This review will include studies investigating stable patients of all ages, diagnosed with a traumatic occult pneumothorax on a CT scan that receive

mechanical ventilation, who were managed with conservative management or ICC insertion.

Methods: Eligible studies will include randomized and non-randomized controlled trials, and prospective and retrospective cohort studies. PubMed, EMBASE, CINAHL, Web of Science and Cochrane Central Register of Controlled Trials will be searched. International clinical trials registry (ICTR), Australian and New Zealand clinical trials registry (ANZCTR) and Clinicaltrials.gov will be searched for unpublished studies. All included studies will be critically appraised using standardised JBI tools, with no exclusions based on methodological quality. Studies will, where possible, be pooled in statistical meta-analysis, with impact of methodological quality to be explored with sensitivity analysis.

Review question

What is the effectiveness and safety of conservative management of occult pneumothorax in mechanically ventilated patients?

Introduction

Occult pneumothorax was first described in 1983-84,[1,2] after pneumothoraces were seen on lung windows from abdominal and head computed tomography (CT scans) that hadn't previously been identified on chest x-rays. The definition of occult pneumothorax has since been refined to air within the pleural cavity that is diagnosed on CT scan but was not suspected on the basis of preceding clinical examination or supine chest x-ray.[3-5] The overall incidence in trauma patients is approximately 5%,[3,4] although an incidence as high as 37% has been reported in some studies.[6-8]

Although occult pneumothorax was first described over 30 years ago, there is no consensus on its best management strategy for occult pneumothorax; this is especially the case with patients receiving mechanical ventilation. The Advanced Trauma Life Support (ATLS) Manual,[9] the primary source globally for medical education on trauma management, recommends that all patients diagnosed with a pneumothorax that receive mechanical ventilation require placement of an intercostal catheter (ICC). The Emergency Trauma Management (ETM) Course

Manual,[10] a recently formed critical care-focused trauma course, is less prescriptive. It states that although classical teaching is to place an ICC for a pneumothorax in a patient undergoing mechanical ventilation, this has been challenged recently and observation may be appropriate. A survey completed in the UK showed there is disagreement between medical specialties that commonly manage this group of patients, with variation from 28% to 100% that would place a prophylactic ICC.[11] The concern with occult pneumothorax in patients receiving mechanical ventilation is the potential risk of progression to a tension pneumothorax, which can be life-threatening. Due to the risk of this life-threatening sequela, prophylactic insertion of an ICC is common. Unfortunately, ICC insertion is not without risk and is associated with a major complication rate of up to 20%.[12,13] Complications include cardiac and vascular injury, intraparenchymal lung injuries, solid organ injuries (including liver and spleen), malpositioning (requiring reinsertion) and infection (empyema and wound infection). These complications do not include the pain involved in both insertion and dwelling, or the large scar that remains. The risk of malpositioning means that ICC insertion does not ensure that the progression to tension pneumothorax can be prevented and may actually delay the diagnosis of tension pneumothorax if it does occur. Patients may be exposed to a higher risk of harm, with the lack of consensus in both teaching of trauma management and between specialities managing these patients leading to a high probability of clinical practice variation.

Inconsistent results reported in research studies investigating management of occult pneumothorax further highlight controversies in this field. A study by Enderson et al[14] included 40 patients with occult pneumothorax and randomized them to observation or ICC placement, of this, 27 received mechanical ventilation (15 in the observation group and 12 in the ICC group). In the observation group, three developed tension pneumothorax and a further five patients had progression of pneumothorax requiring ICC placement. From this study, it was advised that all patients with an occult pneumothorax who require mechanical ventilation receive a prophylactic ICC. More recent studies have shown no tension pneumothoraces and no increased mortality with observation alone in mechanically ventilated patients. These studies have reported a “failure” of observation (defined as requirement for

ICC insertion) between 13-30%.[5,15,16] Despite this apparent high failure rate, the corollary is that at least 70% of patients have avoided an unnecessary procedure.

Similar mechanisms account for pneumothorax caused by blunt and penetrating trauma. In blunt trauma, pneumothorax can occur via three mechanisms.[17] First, direct injury to the pleura by fractured or dislocated ribs. If no rib fractures are present, the suspected mechanism is either rupture of alveoli with the increased pressure caused by sudden chest compression or, uncommonly, increased pressure in the trachea or bronchi with a closed glottis causing rupture in the larger airways. The mechanism of pneumothorax in penetrating trauma is simpler and more direct, with air either entering the pleural cavity from a penetrating wound or direct damage to the lung.[17] As a proportion of the blunt pneumothoraces are caused by a penetrating mechanism from fractured or dislocated ribs, blunt and penetrating trauma will be considered together in our review.

A preliminary search of PROSPERO, PubMed, the *Cochrane Database of Systematic Reviews* and the *JBI Database of Systematic Reviews and Implementation Reports* failed to identify any recent or underway systematic reviews on the topic. One systematic review was identified on the topic of occult pneumothorax by Yadav et al in 2009.[18] These authors investigated the safety of observing occult pneumothorax in all trauma patients, not only those patients receiving mechanical ventilation. They included three RCTs, with variable results for and against the use of conservative management. Since this review there has been more research conducted and published on occult pneumothorax in the patient population requiring mechanical ventilation. The question of conservative management for occult pneumothorax was also briefly mentioned in a larger review on blunt chest trauma in 2015.[19] The review's authors added one RCT and two retrospective cohort studies that showed no difference in terms of length of stay and mortality between observation and ICC insertion for occult pneumothorax. When exposed to mechanical ventilation the authors felt the risk of tension pneumothorax was acceptable, without specifically stating what that risk was.

How to best manage an occult pneumothorax in mechanically ventilated patients is important, as a significant proportion of trauma patients will receive mechanical ventilation either within intensive care or the emergency department or for the

provision of general anaesthesia. This review will identify the best available evidence to evaluate the effectiveness and safety of conservative management compared to ICC insertion for occult pneumothorax in mechanically ventilated patients. The review of available evidence will specifically investigate progression of pneumothorax, incidence of ICC insertion for any reason, incidence of tension pneumothorax and incidence of pneumonia/empyema.

Keywords

Conservative Management; Mechanical Ventilation; Observation; Occult Pneumothorax; Tube Thoracostomy

Inclusion Criteria

Participants

The review will consider studies that include stable patients of any age who are diagnosed with a traumatic occult pneumothorax on thoracoabdominal CT scan and receiving mechanical ventilation. Mechanical ventilation can occur in the emergency department, intensive care unit or as part of the provision of general anaesthesia. The review will consider occult pneumothoraces caused by either blunt or penetrating trauma; occult haemopneumothoraces will be excluded from our review.

Intervention(s)

This review will consider studies that evaluate conservative management/observation for occult pneumothorax. Conservative management includes clinical observation, serial examinations and/or serial chest x-rays.

Comparator(s)

This review will consider studies that compare the intervention to ICC insertion for occult pneumothorax. The ICC can be inserted via any method, including Seldinger technique or blunt dissection.[20]

Outcomes

The primary outcomes of interest are: progression of pneumothorax (seen on chest x-ray), ICC insertion for any reason, incidence of tension pneumothorax (diagnosed clinically) and incidence of pneumonia/empyema

The secondary outcomes of interest are: mortality, ICC insertion (tension pneumothorax), ICC insertion (progression to simple pneumothorax), ICC insertion (non-pneumothorax reasons), length of stay in hospital and intensive care (in days), duration of mechanical ventilation (in days), duration of ICC dwelling (in days), haemodynamic instability (measured as need for vasopressor support), pain (measured by a validated pain scoring tools for sedated ICU patients i.e. Behavioural pain scale (BPS) and Critical-Care Pain Observation Tool (CPOT))[21-23] and analgesia requirements (measured in parenteral morphine equivalents per 24 hours as per ANZCA opioid conversion)[24]

This review will also consider adverse events/complications of ICC insertion (measured as composite and breakdown; including malpositioning, infection, organ injury and vascular injury).

Types of Studies

This review will consider both experimental and quasi-experimental study designs including randomized controlled trials and non-randomized controlled trials. In addition, observational studies including prospective and retrospective cohort studies will be considered for inclusion.

Methods

The proposed systematic review will be conducted in accordance with the Joanna Briggs Institute methodology for systematic reviews of effectiveness evidence.[25]

PROSPERO Registration number: *awaiting registration*

Search Strategy

The search strategy aims to locate both published and unpublished studies. An initial limited search of PubMed was undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles, and the index terms used to describe the articles were used to develop a full search strategy for PubMed (see Appendix 1). The search strategy, including all identified keywords and index

terms, will be adapted for the following databases: PubMed, EMBASE, CINAHL, Web of Science and Cochrane Central Register of Controlled Trials. Sources of unpublished studies will include: The International clinical trials registry (ICTR), Australian and New Zealand clinical trials registry (ANZCTR) and Clinicaltrials.gov. The reference list of all studies selected for inclusion will be screened for additional studies.

Study Selection

Following the search, all identified records will be collated and uploaded into Endnote X8.2 (Clarivate Analytics, PA, USA) and duplicates removed. Titles and abstracts will then be screened by one reviewer (JS) for assessment against the inclusion criteria for the review. Potentially relevant studies will be retrieved in full and their citation details imported into the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI 2017) (Joanna Briggs Institute, Adelaide, Australia).[26] The full text of selected citations will be assessed in detail against the inclusion criteria by one reviewer (JS). Reasons for exclusion of full text studies that do not meet the inclusion criteria will be recorded and reported in the systematic review. Any uncertainties that arise at each stage of the study selection process will be resolved through discussion with a second reviewer (PS, EA). The results of the search and study inclusion process will be reported in full in the final systematic review and presented in a Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram.[27]

Assessment of Methodological Quality

Eligible studies will be critically appraised by two independent reviewers (JS, AV) at the study level for methodological quality in the review using standardized critical appraisal instruments from the Joanna Briggs Institute for experimental, quasi-experimental studies and comparable cohort studies.[25] Authors of papers will be contacted to request missing or additional data for clarification, where required. Any disagreements that arise will be resolved through discussion, or with a third reviewer (PS, EA). The results of critical appraisal of the included studies will be reported in narrative form and in a table.

Given the limited quantity of expected literature in this field, studies will not be excluded based on low methodological quality and high risk of bias, rather, study quality will be considered when analysing and interpreting results.[28]

Data Extraction

Data will be extracted from studies included in the review using a modified standardized data extraction tool[25] (see appendix II). The data extracted will include specific details about the populations, study methods, interventions, and outcomes of significance to the review objective. Outcomes include: progression of pneumothorax, ICC insertion for any reason, incidence of tension pneumothorax, incidence of pneumonia/empyema, ICC insertion (tension pneumothorax), ICC insertion (progression to simple pneumothorax), ICC insertion (non-pneumothorax reasons), length of stay in Hospital and Intensive Care, duration of mechanical ventilation, duration of ICC dwelling, haemodynamic instability, ICC complications (including malpositioning, infection, organ injury and vascular injury), pain and analgesia requirements.

Insertion technique for ICC insertion in both groups will be extracted where possible.

Any uncertainties that arise at each stage of the data extraction process will be resolved through discussion with a second reviewer (PS, EA). Authors of papers will be contacted to request missing or additional data, where required.

Data Synthesis

Studies will, where possible, be pooled in statistical meta-analysis using JBI SUMARI. Effect sizes will be expressed as either odds ratios (for dichotomous data) and weighted (or standardized) final post-intervention mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard chi-squared and I squared tests. The choice of model (random or fixed effects) and method for meta-analysis will be based on the guidance by Tufunaru et al.[29] Experimental and observational data will be synthesised in separate meta-analyses for each outcome. Impact of study quality and differences in sample size, age of patients (adult vs child) and insertion technique (blunt dissection vs Seldinger) will be explored using

sensitivity analysis. Where statistical pooling is not possible the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate. A funnel plot will be generated to assess publication bias if there are 10 or more studies included in a meta-analysis. Statistical tests for funnel plot asymmetry (Egger test, Begg test, Harbord test) will be performed where appropriate.

Assessing Certainty in the Findings

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach for grading the certainty of evidence will be followed[30] and a Summary of Findings (SoF) will be created using GRADEPro GDT 2015 (McMaster University, ON, Canada). The SoF will present the following information where appropriate: absolute risks for the treatment and control, estimates of relative risk, and a ranking of the quality of the evidence based on the risk of bias, directness, heterogeneity, precision and risk of publication bias of the review results.

The outcomes reported in the SoF will be: Progression of pneumothorax, Incidence of ICC insertion for any reason, incidence of tension pneumothorax, incidence of pneumonia/empyema, incidence of ICC complications, ICU and Hospital length of stay, duration of mechanical ventilation and mortality.

Acknowledgements

Vicki Langton and Robert Franchini, University of Adelaide Research Librarians, for their help developing the search strategy for this review.

This review is to contribute towards a Master of Clinical Science for JS.

Funding

There is no funding for this review.

Conflicts of Interest

EA is Editor-in-Chief of JBI Database of Systematic Reviews and Implementation Reports, he has been blinded to the editorial process associated with this manuscript.

References

1. Wall S, Federle M, Jeffrey B, Brett C. CT Diagnosis of Unsuspeted Pneumothorax after Blunt Abdominal Trauma. Am J Roentgenol Radium Ther. 1983; 141(5):919-21.

2. Tocino I, Miller M, Frederick P, Thomas F. CT Detection of Occult Pneumothorax in Head Trauma. Am J Roentgenol Radium Ther. 1984; 143(5):987-90.

3. Ball C, Kirkpatrick A, Feliciano D. The Occult Pneumothorax: What have we learned? Can J Surg. 2009; 52(5):173-9.

4. Omar H, Abdelmalak H, Mangar D, Rashad R, Helal E, Camporesi E. Occult pneumothorax, revisited. J Trauma. 2010; 4(12):1-6.

5. Zhang M, Teo L, Goh M, K G. Occult pneumothorax in blunt trauma: is there a need for tube thoracostomy? Eur J Trauma Emerg Surg. 2016; 42:785-90.

6. Lamb A, Qadan M, Gray A. Detection of occult pneumothoraces in the significantly injured adult with blunt trauma. Eur J Emerg Med. 2007; 14:65-7.

7. Stafford R, Linn J, Washington L. Incidence and management of occult hemothoraces. Am J Surg. 2006; 192:722-6.

8. Charbit J, Millet I, Maury C, Conte B, Roustan J, Taourel P et al. Prevalence of large and occult pneumothoraces in patients with severe blunt trauma upon hospital admission: experience of 526 cases in a French level 1 trauma center. Am J Emerg Med. 2015; 33:796-801.

9. American College of Surgeons. Advanced Trauma Life Support Student Course Manual. 9th ed. Chicargo, USA: Committee on Trauma; 2012.

10. Emergency Trauma Management Pty Ltd. Emergency Trauma Management Course Manual. [cited 4th March 2019]. Available from: https://etmcourse.com

11. Hudson A. Traumatic occult pneumothorax - A UK perspective. Resuscitation. 2011; 82:639.

12. Etoch S, Bar-Natan M, Miller F, Richardson D. Tube Thoracostomy: Factors Related to Complications. Arch Surg. 1995; 130:521-6.

13. Kesieme E, Dongo A, Ezemba N, Irekpita E, Jebbin N, Kesieme C. Tube Thoracostomy: Complications and Its Management. Pulm Med. 2012; 2012:1-10.

14. Enderson B, Abdalla R, Frame S, Casey M, Gould H, Maull L. Tube Thoracostomy for Occult Pneumothorax: A Prospective Randomized Study of it Use. J Trauma. 1993; 35(5):726-30.

15. Moore F, Goslar P, Coimbra R, Velmahos G, Brown C, Coopwood T et al. Blunt Traumatic Occult Pneumothorax: Is Observation Safe? - Results of a Prospective, AAST Multicenter Study. J Trauma. 2011; 70(5):1019-25.

16. Ouellet J, Trottier V, Kmet L, Rizoli S, Laupland K, Ball C et al. The OPTICC trial: a multi-institutional study of occult pneumothoraces in critical care. Am J Surg. 2009; 197:581-6.

17. Milisavljevic S, Spasic M, Arsenijevic M. Thoracic Trauma. In: Cagani L, editor. Current concepts in general thoracic surgery. Rijeka, Croatia: Oliver Kurelic; 2012; p. 198-297.

18. Yadav K, Jalili M, Zehtabchi S. Management of Traumatic occult pneumothorax. Resuscitation. 2010; 81:1063-8.

19. Lesquen H, Avaro J, Gust L, Ford R, Beranger F, Natale C et al. Surgical Management for the first 48 h following blunt chest trauma: state of the art (excluding vascular injuries). Interact Cardiovasc Thorac Surg. 2015; 20(399-408).

20. ACI Respiratory Network. Pleural Drains in Adults - A consensus guideline. 2016 [cited 5th April 2019]. Available from: https://www.aci.health.nsw.gov.au/__data/assets/pdf_file/0018/201906/PleuralDrains_Guideline-021116.pdf

21. Ahlers S, Van Der Veen A, Van Dijk M, Tibboel D, Knibbe C. The Use of the Behavioural Pain Scale to Assess Pain in Concious Sedated Patients. Anesth Analg. 2010; 110(1):127-33.

22. Gélinas C, Fillion L, Puntillo K, Viens C, Fortier M. Validation of the Critical-Care Pain Observation Tool in Adult Patients. Am J Crit Care. 2006; 15(4):420-27.

23. Rijkenberg S, Stilma W, Endeman H, Bosma R, Vann Straaten O. Pain measurement in mechanially ventilated critically ill patients: Behavioral Pain Scale versus Critical-Care Pain Observation Tool. J Crit Care. 2015; 30:167-72.

24. ANZCA Faculty of Pain Medicine. Opioid Dose Equivalence. [cited 14th April 2019]. Available from: https://fpm.anzca.edu.au/documents/opioid-dose-equivalence.pdf

25. Tufanaru C, Munn Z, Armoataris E, Campbell J, Hopp L. Joanna Briggs Institiute Reviewer's Manual. The Joanna Briggs Institute; 2017 [cited 13th April 2019]. Available from: https://reviewersmanual/joannabriggs.org/

26. The Joanna Briggs Institute. The System for the Unfifed Management, Assessment and Review of Information (SUMARI). 2017 [cited March 7 2019]. Available from: https://www.jbisumari.org

27. Moher D, Liberati A, Tetzlaff J, Altman D, The PRISMA Group. Preferred Reporting Items for Systemeatic Reviews and Meta-Analyses: The PRISMA Statement. BMJ. 2009; 339:b2535.

28. Herbison P, Hay-Smith J, Gillespie W. Adjustment of meta-analyses on the basis of quality scores should be abandoned J Clin Epidemiol. 2006; 59:1249-56.

29. Tufanaru C, Munn Z, Stephenson M, Armoataris E. Fixed or random effects meta-analysis? Common methologoical issues in sysematic reviews of effectiveness. Int J Evid Based Healthc. 2015; 13:196-207.

30. Schunemm H, Brozek J, Guyatt G, Oxman A (editors). GRADE Handbook. Handbook for grading the quality of evidence and the strength or recommendations using the GRADE approach. Update October 2013.

Appendix 2: Search strategy

PubMed search strategy

Pneumothorax	Mechanical ventilation	Conservative management Or Intercostal catheter
Pneumothorax[mh] OR pneumothora*[tw] OR collapsed lung[tw]	Artificial respiration[mh] OR Intermittent Positive-Pressure Ventilation[mh] OR Positive Pressure Respiration[mh] OR mechanical ventilation[tw] OR mechanical vent*[tw] OR IPPV[tw] OR intermittent positive-pressure ventilation[tw] OR intermittent positive pressure vent*[tw] OR biphasic intermittent positive airway pressure[tw] OR PPV[tw] OR positive pressure vent*[tw]	Conservative treatment[mh] OR conservative[tw] OR conservative manage*[tw] OR conservative treatment[tw] OR observation[tw] OR observ*[tw] OR expectant manage*[tw] OR managed expectantly[tw] OR watchful waiting[mh] OR Chest tubes[mh] OR chest tube[tw] OR intercostal catheter[tw] OR intercostal tube[tw] OR intercostal drain[tw] OR chest drain[tw] OR ICC[tw] OR chest catheter[tw] OR thoracocentesis[mh] OR thoracocentesis[tw] OR thoracentesis[tw] OR pleurocentesis[mh] OR pleurocentesis[tw] OR chest intubation[tw] OR tube thoracostomy[tw] OR pleural drainage[tw] OR thoracostomy[mh]

(Pneumothorax[mh] OR pneumothora*[tw] OR collapsed lung[tw]) AND (Artificial respiration[mh] OR Intermittent Positive-Pressure Ventilation[mh] OR Positive Pressure Respiration[mh] OR mechanical ventilation[tw] OR mechanical vent*[tw] OR IPPV[tw] OR intermittent positive-pressure ventilation[tw] OR intermittent positive pressure vent*[tw] OR biphasic intermittent positive airway pressure[tw] OR PPV[tw] OR positive pressure vent*[tw]) AND (Conservative treatment[mh] OR conservative[tw] OR conservative manage*[tw] OR conservative treatment[tw] OR observation[tw] OR observ*[tw] OR expectant manage*[tw] OR managed expectantly[tw] OR watchful waiting[mh] OR Chest tubes[mh] OR chest tube[tw] OR intercostal catheter[tw] OR intercostal tube[tw] OR intercostal drain[tw] OR chest drain[tw] OR ICC[tw] OR chest catheter[tw] OR thoracocentesis[mh] OR thoracocentesis[tw] OR thoracentesis[tw] OR pleurocentesis[mh] OR pleurocentesis[tw] OR chest intubation[tw] OR tube thoracostomy[tw] OR pleural drainage[tw] OR thoracostomy[mh])

595 results – 17th June 2019

Embase search strategy

Pneumothorax	Mechanical ventilation	Conservative management Or Intercostal catheter
'Pneumothorax'/exp OR 'pneumothora*':ti,ab OR 'collapsed lung':ti,ab	'artificial ventilation'/exp OR 'intermittent positive pressure ventilation'/exp OR 'artificial respiration':ti,ab OR 'Intermittent Positive-Pressure Ventilation':ti,ab OR 'Positive Pressure Respiration':ti,ab OR 'mechanical ventilation':ti,ab OR 'mechanical vent*':ti,ab OR 'IPPV':ti,ab OR 'intermittent positive pressure vent*':ti,ab OR 'biphasic intermittent positive airway pressure':ti,ab OR 'PPV':ti,ab OR 'positive pressure vent*':ti,ab	'conservative treatment'/exp OR 'intercostal catheter'/exp OR 'Conservative treatment':ti,ab OR 'conservative':ti,ab OR 'conservative manage*':ti,ab OR 'Observation':ti,ab OR 'observ*':ti,ab OR 'Expectant manage*':ti,ab OR 'managed expectantly':ti,ab OR 'watchful waiting':ti,ab OR 'chest tube'/exp OR 'chest tube':ti,ab OR 'intercostal catheter':ti,ab OR 'intercostal tube':ti,ab OR 'intercostal drain':ti,ab OR 'chest drain':ti,ab OR 'ICC':ti,ab OR 'chest catheter':ti,ab OR 'thoracocentesis'/exp OR 'thoracocentesis':ti,ab OR 'thoracentesis':ti,ab OR 'pleurocentesis':ti,ab OR 'chest intubation':ti,ab OR 'tube thoracostomy':ti,ab OR 'pleural drainage':ti,ab OR 'thoracostomy'/exp

('Pneumothorax'/exp OR 'pneumothora*':ti,ab OR 'collapsed lung':ti,ab) AND ('artificial ventilation'/exp OR 'intermittent positive pressure ventilation'/exp OR 'artificial respiration':ti,ab OR 'Intermittent Positive-Pressure Ventilation':ti,ab OR 'Positive Pressure Respiration':ti,ab OR 'mechanical ventilation':ti,ab OR 'mechanical vent*':ti,ab OR 'IPPV':ti,ab OR 'intermittent positive pressure vent*':ti,ab OR 'biphasic intermittent positive airway pressure':ti,ab OR 'PPV':ti,ab OR 'positive pressure vent*':ti,ab) AND ('conservative treatment'/exp OR 'intercostal catheter'/exp OR 'Conservative treatment':ti,ab OR 'conservative':ti,ab OR 'conservative manage*':ti,ab OR 'Observation':ti,ab OR 'observ*':ti,ab OR 'Expectant manage*':ti,ab OR 'managed expectantly':ti,ab OR 'watchful waiting':ti,ab OR 'chest tube'/exp OR 'chest tube':ti,ab OR 'intercostal catheter':ti,ab OR 'intercostal tube':ti,ab OR 'intercostal drain':ti,ab OR 'chest drain':ti,ab OR 'ICC':ti,ab OR 'chest catheter':ti,ab OR 'thoracocentesis'/exp OR 'thoracocentesis':ti,ab OR 'thoracentesis':ti,ab OR 'pleurocentesis':ti,ab OR 'chest intubation':ti,ab OR 'tube thoracostomy':ti,ab OR 'pleural drainage':ti,ab OR 'thoracostomy'/exp)

1694 results – 17th June 2019

CINAHL search strategy

Pneumothorax	Mechanical ventilation	Conservative management Or Intercostal catheter
MH "pneumothorax"+ OR TI "pneumothorax*" OR AB "pneumothorax*" OR TI "collapsed lung" OR AB "collapsed lung"	MH "respiration, artificial"+ OR MH "positive pressure ventilation"+ OR TI "artificial respiration" OR AB "artificial respiration" OR TI "artificial ventilation" OR AB "artificial ventilation" OR TI "intermittent positive pressure ventilation" OR AB "intermittent positive pressure ventilation" OR TI "intermittent positive pressure vent*" OR AB "intermittent positive pressure vent*" OR TI "positive pressure respiration" OR AB "positive pressure respiration" OR TI "mechanical ventilation" OR AB "mechanical ventilation" OR TI "mechanical vent*" OR AB "mechanical vent*" OR TI "IPPV" OR AB "IPPV" OR TI "PPV" OR AB "PPV" OR TI "positive pressure vent*" OR AB "positive pressure vent*" OR TI "biphasic intermittent positive airway pressure" or AB "biphasic intermittent positive airway pressure"	MH "Thoracostomy"+ OR MH "chest tubes"+ OR TI "chest tube" OR AB "chest tube" OR TI "chest drain" OR AB "chest drain" OR TI "intercostal catheter" OR AB "intercostal catheter" OR TI "intercostal drain" OR AB "intercostal drain" OR TI "intercostal tube" OR AB " intercostal tube" OR TI "chest catheter" OR AB "chest catheter" OR TI "ICC" OR AB "ICC" OR TI "thoracocentesis" OR AB "thoracocentesis" OR TI "thoracentesis" OR AB "thoracentesis" OR TI "pleurocentesis" OR AB "pleurocentesis" OR TI "chest intubation" OR AB "chest intubation" OR TI "tube thoracostomy" OR AB "tube thoracostomy" OR TI "pleural drainage" OR AB "pleural drainage" OR TI "thoracostomy" OR AB "thoracostomy" OR TI "conservative treatment" OR AB "conservative treatment" OR TI "conservative" OR AB "conservative" OR TI "conservative manage*" OR AB "conservative mange*" OR TI "observation" OR AB "observation" OR TI "observ*" OR AB "observ*" OR TI "expectant manage*" OR AB "expectant manage*" OR TI "manage expectantly" OR AB "manage expectantly" OR TI "watchful waiting" OR AB "watchful waiting"

(MH “pneumothorax”+ OR TI “pneumothorax*” OR AB “pneumothorax*” OR TI “collapsed lung” OR AB “collapsed lung”) AND (MH “respiration, artificial”+ OR MH “positive pressure ventilation”+ OR TI “artificial respiration” OR AB “artificial respiration” OR TI “artificial ventilation” OR AB “artificial ventilation” OR TI “intermittent positive pressure ventilation” OR AB “intermittent positive pressure ventilation” OR TI “intermittent positive pressure vent*” OR AB “intermittent positive pressure vent*” OR TI “positive pressure respiration” OR AB “positive pressure respiration” OR TI “mechanical ventilation” OR AB “mechanical ventilation” OR TI “mechanical vent*” OR AB “mechanical vent*” OR TI “IPPV” OR AB “IPPV” OR TI “PPV” OR AB “PPV” OR TI “positive pressure vent*” OR AB “positive pressure vent*” OR TI “biphasic intermittent positive airway pressure” or AB “biphasic intermittent positive airway pressure”) AND (MH “Thoracostomy”+ OR MH “chest tubes”+ OR TI “chest tube” OR AB “chest tube” OR TI “chest drain” OR AB “chest drain” OR TI “intercostal catheter” OR AB “intercostal catheter” OR TI “intercostal drain” OR AB “intercostal drain” OR TI “intercostal tube” OR AB “ intercostal tube” OR TI “chest catheter” OR AB “chest catheter” OR TI “ICC” OR AB “ICC” OR TI “thoracocentesis” OR AB “thoracocentesis” OR TI “thoracentesis” OR AB “thoracentesis” OR TI “pleurocentesis” OR AB “pleurocentesis” OR TI “chest intubation” OR AB “chest intubation” OR TI “tube thoracostomy” OR AB “tube thoracostomy” OR TI “pleural drainage” OR AB “pleural drainage” OR TI “thoracostomy” OR AB “thoracostomy” OR TI “conservative treatment” OR AB “conservative treatment” OR TI “conservative” OR AB “conservative” OR TI “conservative manage*” OR AB “conservative mange*” OR TI “observation” OR AB “observation” OR TI “observ*” OR AB “observ*” OR TI “expectant manage*” OR AB “expectant manage*” OR TI “manage expectantly” OR AB “manage expectantly” OR TI “watchful waiting” OR AB “watchful waiting”)

97 results – 17th June 2019

Web of Science search strategy

Pneumothorax	Mechanical ventilation	Conservative management Or Intercostal catheter
TS=(pneumothora* OR "collapsed lung")	TS=("mechanical ventilation" OR "mechanical vent*" OR "IPPV" OR "PPV" OR "intermittent positive-pressure vent*" OR "intermittent positive pressure vent*" OR "biphasic intermittent positive airway pressure" OR "positive pressure vent*" OR "artificial respiration" OR "positive pressure respiration")	TS=("conservative treatment" OR "conservative" OR "conservative mange*" OR "observation" OR "observe*" OR "expectant manage*" OR "manage expectantly" OR "watchful waiting" OR "chest tube" OR "chest drain" OR "chest catheter" OR "chest intubation" OR "intercostal catheter" OR "intercostal drain" OR "intercostal tube" OR "ICC" OR "thoracocentesis" OR "thoracentesis" OR "pleurocentesis" OR "tube thoracostomy" OR "pleural drainage" OR "thoracostomy")

TS=(pneumothora* OR "collapsed lung") AND TS=("mechanical ventilation" OR "mechanical vent*" OR "IPPV" OR "PPV" OR "intermittent positive-pressure vent*" OR "intermittent positive pressure vent*" OR "biphasic intermittent positive airway pressure" OR "positive pressure vent*" OR "artificial respiration" OR "positive pressure respiration") AND TS=("conservative treatment" OR "conservative" OR "conservative mange*" OR "observation" OR "observe*" OR "expectant manage*" OR "manage expectantly" OR "watchful waiting" OR "chest tube" OR "chest drain" OR "chest catheter" OR "chest intubation" OR "intercostal catheter" OR "intercostal drain" OR "intercostal tube" OR "ICC" OR "thoracocentesis" OR "thoracentesis" OR "pleurocentesis" OR "tube thoracostomy" OR "pleural drainage" OR "thoracostomy")

566 results – 17th June 2019

Cochrane Central Register of Controlled Trials search strategy

Pneumothorax	Mechanical ventilation	Conservative management Or Intercostal catheter
[mh pneumothorax] OR 'pneumothora*':ti,ab OR 'collapsed lung':ti,ab	[mh "respiration, artificial"] OR [mh "ventilators, mechanical"] OR [mh "positive-pressure respiration"] OR [mh "intermittent positive-pressure ventilation"] OR [mh "intermittent positive-pressure breathing"] OR 'artificial respiration':ti,ab OR 'Intermittent Positive-Pressure Ventilation':ti,ab OR 'Positive Pressure Respiration':ti,ab OR 'mechanical ventilation':ti,ab OR 'mechanical vent*':ti,ab OR 'IPPV':ti,ab OR 'intermittent positive pressure vent*':ti,ab OR 'biphasic intermittent positive airway pressure':ti,ab OR 'PPV':ti,ab OR 'positive pressure vent*':ti,ab	[mh "chest tubes"] OR [mh "thoracentesis"] OR [mh "thoracostomy"] OR [mh "conservative treatment"] OR [mh "observation"] OR [mh "watchful waiting"] OR 'Conservative treatment':ti,ab OR 'conservative':ti,ab OR 'conservative manage*':ti,ab OR 'Observation':ti,ab OR 'observ*':ti,ab OR 'Expectant manage*':ti,ab OR 'managed expectantly':ti,ab OR 'watchful waiting':ti,ab OR 'chest tube':ti,ab OR intercostal catheter':ti,ab OR 'intercostal tube':ti,ab OR 'intercostal drain':ti,ab OR 'chest drain':ti,ab OR 'ICC':ti,ab OR 'chest catheter':ti,ab OR 'thoracocentesis':ti,ab OR 'thoracentesis':ti,ab OR 'pleurocentesis':ti,ab OR 'chest intubation':ti,ab OR 'tube thoracostomy':ti,ab OR 'pleural drainage':ti,ab

([mh pneumothorax] OR 'pneumothora*':ti,ab OR 'collapsed lung':ti,ab) AND ([mh "respiration, artificial"] OR [mh "ventilators, mechanical"] OR [mh "positive-pressure respiration"] OR [mh "intermittent positive-pressure ventilation"] OR [mh "intermittent positive-pressure breathing"] OR 'artificial respiration':ti,ab OR 'Intermittent Positive-Pressure Ventilation':ti,ab OR 'Positive Pressure Respiration':ti,ab OR 'mechanical ventilation':ti,ab OR 'mechanical vent*':ti,ab OR 'IPPV':ti,ab OR 'intermittent positive pressure vent*':ti,ab OR 'biphasic intermittent positive airway pressure':ti,ab OR 'PPV':ti,ab OR 'positive pressure vent*':ti,ab) AND ([mh "chest tubes"] OR [mh "thoracentesis"] OR [mh "thoracostomy"] OR [mh "conservative treatment"] OR [mh "observation"] OR [mh "watchful waiting"] OR 'Conservative treatment':ti,ab OR 'conservative':ti,ab OR 'conservative manage*':ti,ab OR 'Observation':ti,ab OR 'observ*':ti,ab OR 'Expectant manage*':ti,ab OR 'managed expectantly':ti,ab OR 'watchful waiting':ti,ab OR 'chest tube':ti,ab OR intercostal catheter':ti,ab OR 'intercostal tube':ti,ab OR 'intercostal drain':ti,ab OR 'chest drain':ti,ab OR 'ICC':ti,ab OR

‘chest catheter’:ti,ab OR ‘thoracocentesis’:ti,ab OR ‘thoracentesis’:ti,ab OR ‘pleurocentesis’:ti,ab OR ‘chest intubation’:ti,ab OR ‘tube thoracostomy’:ti,ab OR ‘pleural drainage’:ti,ab)

103 results– 17th June 2019

International Clinical Trial Registry search strategy

(http://apps.who.int/trialsearch/AdvSearch.aspx)

Advanced Search
In Title: Pneumothorax OR pneumothoraces
104 results – 17th June 2019

Australian and New Zealand Clinical Trial Registry Search Strategy

(https://www.anzctr.org.au/TrialSearch.aspx)

Advanced Search:
pneumothorax OR pneumothoraces
87 results – 17th June 2019

Clinicaltrials.gov search strategy

(https://clinicaltrials.gov/ct2/search/advanced?cond=&term=&cntry=&state=&city=&dist=)

Advanced Search
In Condition: (pneumothorax OR pneumothoraces)
110 results – 17th June 2019

Appendix 3: Excluded studies and reasons for their exclusion

Article/trial	Barrios C, Tran T, Malinoski D, Lekawa M, Dolich M, Lush S, et al. Successful management of occult pneumothorax without tube thoracostomy despite positive pressure ventilation. The American Surgeon. 2008;74(10):958–61.
Reason for exclusion	No comparison group; study was set up to examine patients who were managed without an ICC. "Medical records were then reviewed to identify patients in which management without immediate tube thoracostomy was attempted."

Article/trial	Moore FO, Goslar PW, Coimbra R, Velmahos G, Brown CVR, Coopwood TB, et al. Blunt traumatic occult pneumothorax: Is observation safe? - results of a prospective, AAST multicenter study. Journal of Trauma - Injury, Infection and Critical Care. 2011;70(5):1019–25.
Reason for exclusion	No comparison group; prospective study undertaken to identify patients with occult pneumothorax. Only followed patients who underwent observation. "Patients were classified according to whether they received immediate tube thoracostomy or underwent observation. The observed patients were followed until hospital discharge." Study then examined differences between those who were successfully observed and those who were not.

Article/trial	University of Calgary, CHU de Quebec-Universite Laval, Sunnybrook Health Sciences Centre, Canadian Intensive Care Foundation, London Health Sciences Centre. Management of Occult Pneumothoraces in Mechanically Ventilated Patients. 2006.
Reason for exclusion	Trial currently underway, in recruitment stages.

Article/trial	Kirkpatrick AW, vanWijngaarden Stephens M, Fabian T. Canadian Association of General Surgeons and American College of Surgeons Evidence Based Reviews in Surgery. 18 - Treatment of occult pneumothoraces from blunt trauma. Canadian Journal of Surgery. 2006;49(5):358–61.
Reason for exclusion	Commentary on previously published randomised controlled trial (Brasel et al.).

Article/trial	Lamb ADG, Qadan M, Gray AJ. Detection of occult pneumothoraces in the significantly injured adult with blunt trauma. European Journal of Emergency Medicine. 2007;14(2):65–7.
Reason for exclusion	No relevant data; study examined incidence of occult pneumothorax and impact of detection on subsequent management. Did not examine outcome differences of management of occult pneumothorax. Also, all patients with occult pneumothoraces receiving mechanical ventilation were treated with an ICC.

Article/trial	Kaiser M, Whealon M, Barrios C, Dobson S, Malinoski D, Dolich M, et al. The clinical significance of occult thoracic injury in blunt trauma patients. The American Surgeon. 2010;76(10):1063–6.
Reason for exclusion	No relevant data; study examined incidence of occult thoracic injuries and outcomes between occult and overt thoracic injuries. Management of occult pneumothorax not included in study.

Article/trial	Johnson G. Traumatic pneumothorax: is a chest drain always necessary? Journal of Accident and Emergency Medicine. 1996;13(3):173–4.
Reason for exclusion	No relevant data; retrospective study examining the management of traumatic pneumothorax, however no mention of occult pneumothorax. "Small" and "minimal" used to describe some pneumothoraces in study, however no mention of how these were quantified or if all patients received CT scans.

Article/trial	Wolfman NT, Gilpin JW, Bechtold RE, Meredith JW, Ditesheim JA. Occult pneumothorax in patients with abdominal trauma: CT studies. Journal of Computer Assisted Tomography. 1993;17(1):56–9.
Reason for exclusion	No relevant data; study examined different management strategies for their subclasses of occult pneumothorax. Only minuscule group would be appropriate based on management strategy, however no data available on which patients were mechanically ventilated.

Article/trial	Walker S, Barratt S, Thompson J, Maskell N. Conservative Management in Traumatic Pneumothoraces: An Observational Study. Chest. 2018 153(4): 946-953
Reason for exclusion	No relevant data; data for occult pneumothoraces not separated out in article and author not contactable due to undeliverable email address.

Appendix 4: Critical appraisal explanatory tables

Randomised controlled trials

1. Was true randomization used for assignment of participants to treatment groups?

Yes	Clear explanation of how randomization was achieved and would lead to true randomization
No	Assignment was not random
Unclear	Words 'random' or 'randomisation' used, but vague or unclear explanation of how this was achieved

2. Was allocation to treatment groups concealed?

Yes	Methods used to ensure allocator was unaware of which group patient would be allocated to AND allocator was unlikely to be aware of order of allocation
No	Allocator aware of group that patient would be assigned or could reasonably figure it out
Unclear	Unclear or insufficient information provided on allocation concealment

3. Were treatment groups similar at baseline?

Yes	Groups similar at baseline in at least the following categories o Age o Sex o Severity of trauma (i.e. injury severity score -ISS)
No	Statistically significant difference in above baseline characteristics
Unclear	Baseline characteristics not stated or incomplete

4. Were participants blind to treatment assignment?

Yes	
No	Due to exposure/intervention not possible to blind participants
Unclear	

5. Were those delivering treatment blind to treatment assignment?

Yes	
No	Due to exposure/intervention not possible to blind those delivering treatment
Unclear	

6. Were outcomes assessors blind to treatment assignment?

Yes	Clear explanation of how assessors were blinded to treatment assignment
No	Assessors not blinded to treatment allocation
Unclear	No or unclear explanation of how assessors were blinded to treatment assignment

7. Were treatment groups treated identically other that the intervention of interest?

Yes	Other than intervention of interest, was same standard of care provided to each group
No	Stated clear differences in treatment of groups
Unclear	Treatment other than intervention not clearly stated

8. Was follow up completed and if not, were differences between groups in terms of their follow up adequately described and analysed?

Yes	Number of patients lost to follow up and reason in each group stated AND how loss to follow up altered results analysed
No	No explanation of loss of follow up or significance of this loss
Unclear	Unclear why loss to follow up occurred and unclear how this altered results

9. Were participants analysed in the groups to which they were randomised?

Yes	patient analysed on intention to treat
No	Participants not analysed in groups they were allocated
Unclear	Unclear if patients were analysed in the group they were randomised to

10. Were outcomes measured in the same way for treatment groups?

Yes	Clear definition of outcomes and clear description of how outcomes were to be measured, using validated tools were applicable
No	Inappropriate or non-validated tools used, or different methods used in each group
Unclear	Unclear how outcomes were measured

11. Were outcomes measured in a reliable way?

Yes	the measurement can be easily reproduced
No	Outcomes measured in a way that can't easily be reproduced
Unclear	Unclear how outcomes were measured

12. Was appropriate statistical analysis used?

Yes	Appropriate statistical methods used, which were adequately described and reported.
No	Inappropriate tests used or methods not described.
Unclear	Unclear explanation of method of statistical analysis

13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?

Yes	Was the design appropriate for the question the trial was seeking to answer AND were any deviations from standard RCT design clearly described
No	Question clearly would have been answered better with another study design
Unclear	Unclear why deviations from standard RCT occurred or how these effected results

Include All studies will be included	Exclude	Further information required	Possibly contains subgroup data
Comments (please include: areas that require further information, areas where there are methodological flaws, strengths and weaknesses of trial)			

Cohort studies

1. Were the two groups similar and recruited from the same population?

Yes	All patients were recruited from same population i.e. trauma patients
No	Patients in two groups recruited from different populations
Unclear	Unclear explanation of where patients recruited from

2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?

Yes	Can only be yes, as exposure is occurrence or non-occurrence of a procedure (i.e. intercostal catheter insertion)
No	
Unclear	

3. Was the exposure measured in a valid and reliable way?

Yes	Can only be yes, as exposure is occurrence or non-occurrence of a procedure (i.e. intercostal catheter insertion)
No	
Unclear	

4. Were confounding factors identified?

Yes	Clear description of confounding factors
No	No effort made to describe possible confounders
Unclear	Vague description of possible confounders

5. Were strategies to deal with confounding factors stated?

Yes	Clear description of how confounders were dealt with
No	No description of how confounders were dealt with
Unclear	Vague description of strategies used

6. Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?

Yes	Participants free of intercostal catheter prior to diagnosis of occult pneumothorax
No	Some participants had intercostal catheter in prior to diagnosis of occult pneumothorax
Unclear	Unclear timing of intercostal catheter insertion and diagnosis of occult pneumothorax

7. Were the outcomes measured in a valid and reliable way?

Yes	The measurement can be easily reproduced AND clearly describes outcomes and measured in a standardised way using validated tools were appropriate
No	Outcomes measured in a way that cannot easily be reproduced, using inappropriate or non-standardised way
Unclear	Unclear how outcomes were measured

8. Was the follow-up time reported and sufficient to be long enough for outcomes to occur?

Yes	Follow-up time was reported i.e. 'to hospital discharge'
No	Follow-up time not reported or a period of time shorter than 'to hospital discharge'
Unclear	Vague explanation of follow up time

9. Was follow-up complete, and if not, were reasons to loss to follow-up described and explored?

Yes	Clear description of how many lost to follow-up and reasons for this
No	No description of why lost to follow-up
Unclear	Partial description of either how many or why lost to follow-up

10. Were strategies to address incomplete follow-up utilised?

Yes	Clearly described how incomplete follow-up may affect results
No	No explanation of how incomplete follow-up may affect results
Unclear	Vague explanation of how incomplete follow-up affected results

11. Was appropriate statistical analysis used?

Yes	Appropriate statistical methods used, which were adequately described and reported.
No	Inappropriate tests used or methods not described.
Unclear	Unclear explanation of method of statistical analysis

Include All studies will be included	Exclude	Further information required	Possibly contains subgroup data
Comments (please include: areas that require further information, areas where there are methodological flaws, strengths and weaknesses of trial)			

Appendix 5: Correspondence

Below is the standardised email sent out to corresponding authors of studies published within the last 10 years.

Dear …

I am writing to you in regard to your publication…

I am a Master of Clinical Sciences candidate at the University of Adelaide, and an intensive care registrar in Melbourne, Australia.
As part of my degree I am conducting a systematic review examining the safety and effectiveness of conservative management of occult pneumothorax in mechanically ventilated patients. Your article may contain data that is relevant to this.

The protocol for the systematic review has been published, and is available at: https://journals.lww.com/jbisrir/Abstract/onlinefirst/Effectiveness_and_safety_of_conservative.99815.aspx

I was hoping it would be possible for you to forward data from the subgroup of ventilated patients with occult pneumothoraces, that could be included in a meta-analysis.
The data that is of interested includes:

1. Incidence of pneumothorax progression (and how this was measured)
2. Incidence of tension pneumothorax
3. Incidence of pneumonia/ empyema
4. Incidence of ICC insertion (including reason for insertion)
5. Mortality
6. ICC complications (including type)
7. Haemodynamic instability
8. ICU and Hospital length of stay (in days)

9. ICC dwelling time (in days)
10. Mechanical ventilation duration (in days)
11. Pain scores (using validated tool i.e. Behavioural pain scale (BPS) and Critical-Care Pain Observation Tool (CPOT))
12. analgesia requirement (dose in morphine equivalent per 24 hours)

If you have any description for insertion technique of ICC and type of CT scanner (and thickness of slices) used that would also be useful for my research.

Data presented as mean and SD or median and IQR would be of most value, although if it's easier to send raw data this would also be appreciated.

To help better understand your study I was also hoping you would be able to clarify some details for me.

1.

Many thanks in advance

Dr Jeremy Smith

Fulton & Bratu 2015[167]

Courtney Fulton <cfulton@ualberta.ca> Sat, Feb 8, 8:39 AM

to me

Hi Dr. Smith,

After your first email I reached out to my supervisor and she did not want to provide any raw data. However hopefully I can answer your questions
7) hemodynamic instability was clinically defined by the team taking care of the patient. All our patients were in PICU so were therefore on constant monitoring and had daily chest x rays. Any significant change in vital signs would be noted right away but given this is a retrospective review we did not have parameters in place and it was at the discretion of the treating team
9) Days with chest tubes
Mean for all patients (including no chest tubes at all): 3.35 (range 0-40) days
Mean for only patients with chest tubes: 4.64 days (range 0.4-40) median = 4
11+12) these were not measured in the study.
Chest tubes were inserted (at least in our hospital) by residents or attendings in general surgery with fairly standard technique however in our study documentation was poor and I don't have many details. Also many chest tubes were inserted outside of our facility and for those I have no insertion technique data at all. I do not have the data on the CT scan thickness slices.

Hope this helps.
Courtney

Kirkpatrick et al. 2012[65]

Andrew Kirkpatrick <Andrew.Kirkpatrick@albertahealthservices.ca> Fri, Feb 7, 3:51 PM

to Kevin, me

Jeremy

Overwhelmed with an immediate deadline, but I will try to reply by this weekend,

Andy K

Andrew W Kirkpatrick CD MD MHSc FRCSC FACS
Professor of Surgery and Critical Care Medicine
General, Acute Care, Abdominal Wall Reconstruction, and Trauma Surgery
Foothills Medical Centre, Calgary, Alberta

Andrew Kirkpatrick Thu, Feb 20, 9:46 PM

to Jimmy, Derek, me

Jeremy

Apologies again,

I found your email while searching other data?

I'm asking my colleague Dr Roberts his opinion.

I think e can give you previous data from our interim publication, but not the whole data set as we are just preparing a 150 pt report which will be the final for the AAST

Derek, does that make sense?

Andy

Andrew W Kirkpatrick CD MD MHSc FRCSC FACS
Professor of Surgery and Critical Care Medicine
General, Acute Care, Abdominal Wall Reconstruction, and Trauma Surgery
Foothills Medical Centre, Calgary, Alberta

Derek Roberts Fri, Feb 21, 1:58 AM
to Andrew, me, Jimmy

Hello Jeremy,

Thank you for your e-mail.

I agree with Dr. Kirkpatrick. All of the data that you would require has been published. Did you have a specific question about the data/results that you needed clarified for your systematic review?

D.

--

Derek J. Roberts, BSc (Pharm), MD, PhD, FRCSC

Division of Vascular and Endovascular Surgery
Department of Surgery, University of Ottawa

The Ottawa Hospital, Civic Campus

Jeremy Smith <jeremysmith.tas@gmail.com> Feb 23, 2020, 4:19 PM
to Derek

Hi

Thank you for taking the time to reply.

I agree there is very little data that I haven't been able to get from the article, it is easily the most thorough study on this topic.

I just had a couple of questions.
- Were there any ICC complications that occurred in the 10 patients that had ICCs inserted in the observation group?
- Was any data collected on haemodynamic instability, analgesia requirements or pain?

Also I was wondering if you have an idea of when your final report will be published?

Thanks

Jeremy

Derek Roberts Feb 23, 2020, 4:23 PM
to Andy, me

Hello Jeremy,

ICC? Sorry, what does this abbreviation mean?

No data were collected that weren't reported.

The final results will be submitted to this year's American Association for the Surgery of Trauma meeting, and will be presented there. As per their rules, the manuscript will be published in J Trauma Acute Care Surg.

Best,

D.

--

Derek J. Roberts, BSc (Pharm), MD, PhD, FRCSC

Fellow, Division of Vascular and Endovascular Surgery
Department of Surgery, University of Ottawa

The Ottawa Hospital, Civic Campus

Jeremy Smith <jeremysmith.tas@gmail.com> Feb 23, 2020, 4:59 PM
to Derek

Thanks

Sorry ICC = intercostal catheter or chest drain

Jeremy

Lee et al. 2009[16]

No reply after multiple attempts to contact author.

Notrica et al. 2012[183]

Notrica, David Sat, Jan 11, 1:57 AM
to me

Jeremy

This was actually a subgroup analysis using data from the AAST's OPTX trial. Forrest "Del" Moore was the PI on the study and he has the original data.

DN

David M Notrica, MD FACS FAAP
Trauma Medical Director
Phoenix Children's Hospital
Program Director
Mayo Clinic/Phoenix Children's Hospital Pediatric Surgery Fellowship
Associate Professor of Surgery
Mayo Clinic
Professor of Child Health
University of Arizona College of Medicine Phoenix

Multiple attempts were made to contact Dr Moore for further data with no response.

Zhang et al. 2016[10]

Margaret Zhang <margaret.zhangrx@gmail.com> Fri, Feb 7, 4:32 PM
to me

Hey I'm sorry but I did that study as a medical student and I no longer have the data!

Thanks

Llaquet Bayo et al. 2014[182]

heura ivy <heura.ivy@gmail.com> Tue, Jan 7, 8:08 AM
to me

Dear Dr Smith,

Thank you for contacting me and congratulations for conducting a systematic review about this topic.
I tried to do the same two years ago for my final dissertation in Trauma Science MSc and at that moment there was little quality data and I decided to not publish it. So, I really think it is very interesting to update the existing evidence and I will be happy to read your review. :)

I am going to forward all data as soon as possible (one week) but I am sorry to let you know that I do not have some of the data that you request (p.e. Pain scores).

Dr Heura Llaquet Bayo

heura ivy <heura.ivy@gmail.com> Jan 22, 2020, 3:39 AM

to me

Dear Dr.Smith

I forward data from the subgroup of ventilated patients with occult pneumothoraces in our study ([Results of conservative treatment in patients with occult pneumothorax].
Llaquet Bayo H, Montmany Vioque S, Rebasa P, Navarro Soto S. Cir Esp. 2016 Apr;94(4):232-6. doi: 10.1016/j.ciresp.2015.01.010. Epub 2015 Mar 21. PMID:25804518):

Total number of ventilated patients with occult pneumothoraces: 42 patients. Of those 16 were observed (no ICC) and 26 had an intercostal catheter inserted.

There is a table attached with the incidence of the different items that you asked. I have completed all the areas on the list although some of the information is on the text of the article because it is in Spanish. Unfortunately I do not have information available about items 9 to 12.

Thank you for contacting me and please let me know if you need any other information.

Dr. Heura Llaquet Bayo

1. Incidence of pneumothorax progression (and how this was measured) Measured by plain Rx
2. Incidence of tension pneumothorax
3. **Incidence of pneumonia/ empyema**
4. Incidence of ICC insertion (including reason for insertion
5. Mortality
6. **ICC complications (including type) 1** catheter subcutaneous, 1 loss of catheter (loose fixation)
7. **Haemodynamic instability (including how measured/defined) Defined by Systolic blood pressure<90 or Heart Rate>100 on the primary survey**
8. ICU and Hospital length of stay (in days)
9. **ICC dwelling time (in days):** Information not available
10. **Mechanical ventilation duration (in days):** Information not available
11. **Pain scores (using validated tool i.e. behavioural pain scale (BPS) and Critical-Care Pain Observation Tool (CPOT)):** Information not available
12. **Analgesia requirement (dose in morphine equivalent per 24 hours):** Information not available

	ICC (26)	No ICC (16)
Pneumothorax progression	0	1
Tension pneumothorax	1	0
Pneumonia/Empyema	9	5
Incidence of ICC insertion	26*	3**
Mortality	8	3
ICC complications	2***	0
Haemodynamic instability (SBP<90 o HR>100)	14	9
ICU length of stay (in days) median (IQR)	16,1 (6,7-22,8)	8,4 (7-20,3)
Hospital length of stay (in days) median (IQR)	19,5 (6,4-28,4)	17,2 (8,3-27,9)
ICC dwelling time (in days):	NA	NA
Mechanical ventilation duration (in days):	NA	NA
Pain scores	NA	NA
Analgesia requirement	NA	NA

*Indications of ICC insertion: hemothorax (14), haemodynamic instability (2), patient ventilated (9), big size (1)

**Causes of ICC insertion in patients initially observed: 1 hemothorax, 1 pneumothorax progression, 1 previously to orthopaedic surgery
***Complications of ICC Insertion: one catheter subcutaneous, one loss of catheter (loose fixation)
NA: not available

Jeremy Smith <jeremysmith.tas@gmail.com> Tue, Jan 28, 2:05 PM

to heura

Hi

Thank you so much for this information.

I just had one questions from the data.
The tension pneumothorax that occurred in the ICC group, did this occur before or after ICC insertion and if after ICC insertion how was it managed?

Many thanks

Jeremy

heura ivy <heura.ivy@gmail.com> Feb 6, 2020, 11:12 PM

to me

Hi again,

The tension pneumothorax that occurred in the ICC group was after ICC insertion.

This is the information I have from the patient's file:

Primary survey in the emergency room: Patient on mechanical ventilation FiO2 0.3 SatO2 99% (intubation at scene because a traumatic brain injury with a Glasgow score of 8), FR 18. Chest x-ray: left rib fractures (3rd to 5th), slight hemothorax (but not pneumothorax). After primary survey, a thoraco-abdominal CT scan was performed and a left hemo-pneumothorax was observed. In that moment a left ICC was inserted, with an initial drainage of 1000ml hemothorax. Good control chest x-ray.
Patient was maintained on mechanical ventilation at ICU. But 48 hours after, the patient presented hemodynamic instability, severe hypoxemia, bradycardia and global hypofonesis of the left hemithorax. In that moment a tension pneumothorax was suspected and two more ICC (basal and apical) were inserted. Good evolution, with correct parenchyma reexpansion and improvement of SatO2. ICC were removed seven days later .

Heura Llaquet

Wilson et al. 2009[184]

No reply after multiple attempts to contact author.

Excluded Studies

Walker et al. 2018[178]

postmaster@nbt.nhs.uk via smtp1.e.amses.net Mon, Jan 6, 2:40 PM

to me

Delivery has failed to these recipients or groups:

juilian.thompson@nbt.nhs.uk
The email address that you entered couldn't be found. Check the address and try resending the message. If the problem continues, please contact your helpdesk.

No other contact details available.

Appendix 6: Data extraction tool

Data extraction tool for experimental/observational studies

Modified from JBI data extraction tool[143]

Reviewer _____ Date_____

Primary Author _____ Year_____

Journal _____ Record number _____

Study Methods

RCT ☐ Quasi-RCT ☐

Prospective observational ☐ Retrospective observational ☐

Participants

Country _____

Age_____

group_____

Sample Size

Observation _____ ICC group _____

Notes

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

_____

Study results

Dichotomous data

Outcome	Conservative Management	ICC
Progression of Pneumothorax		
Tension pneumothorax		
Incidence of pneumonia/empyema		
ICC insertion (any reason)		
ICC insertion (tension pneumothorax)		
ICC insertion (progression to simple pneumothorax)		
ICC insertion (non-pneumothorax reason)		
Mortality		
Haemodynamic instability		
ICC complication (composite)		
ICC complication (malpositioning)		
ICC complication (infection)		
ICC complication (organ injury)		
ICC complication (vascular injury)		
Insertion technique (Seldinger / blunt dissection)		

Continuous Data

Outcome	Conservative Management	ICC
ICU length of stay		
Hospital length of stay		
Mechanical ventilation duration		
Duration of ICC dwelling		
Pain		
Analgesia Requirements		

Appendix 7: Sensitivity analysis

7.1 Primary outcomes

7.1.1 Progression of pneumothorax

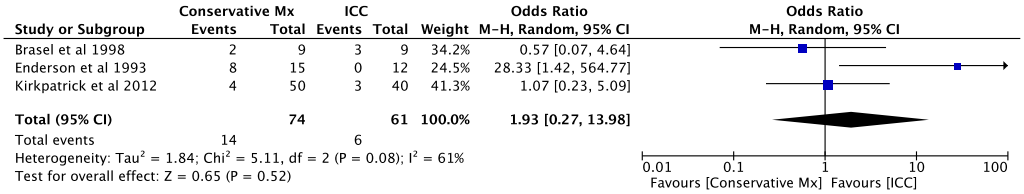


Figure 7.1: Randomised controlled trial progression of pneumothorax M-H forest plot (refer to Figure 3.2)

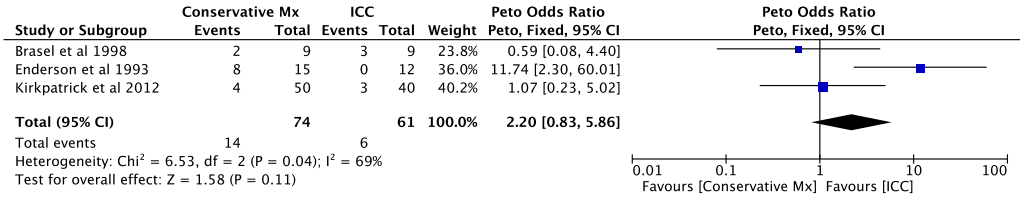


Figure 7.2: Randomised controlled trial progression of pneumothorax Peto odds ratio forest plot (refer to Figure 3.2)

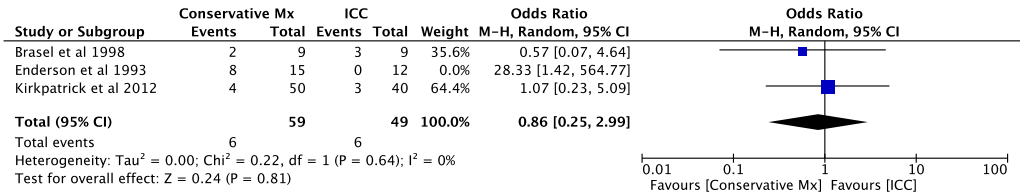


Figure 7.3: Randomised controlled trial progression of pneumothorax without Enderson M-H forest plot (refer to Section 3.4.1.1)

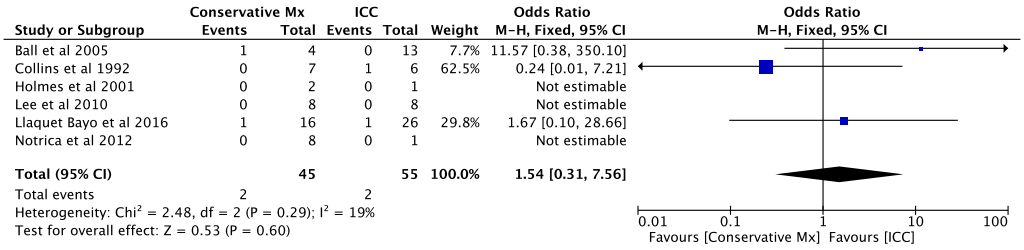


Figure 7.4: Cohort study progression of pneumothorax M-H forest plot (refer to Figure 3.3)

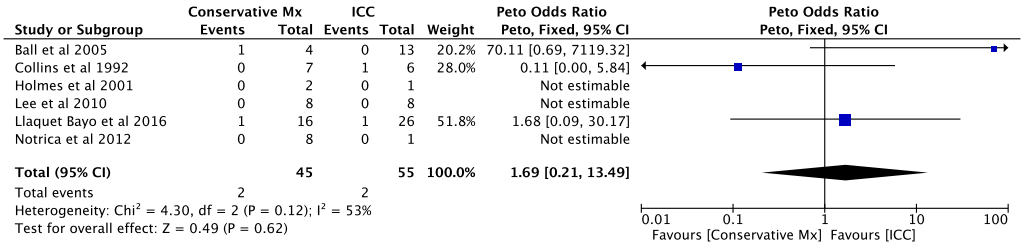


Figure 7.5: Cohort study progression of pneumothorax Peto odds ratio forest plot (refer to Figure 3.3)

7.1.2 Intercostal catheter insertion (any reason)

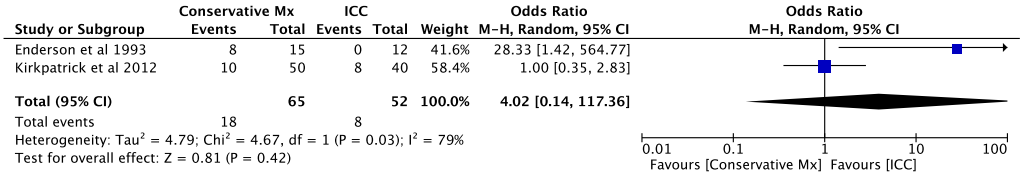


Figure 7.6: Randomised controlled trial intercostal catheter insertion (any reason) M-H forest plot (refer to Figure 3.4)

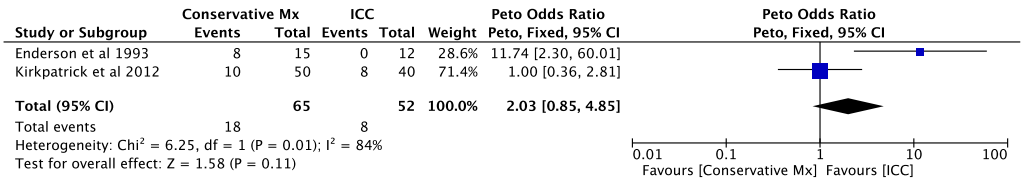


Figure 7.7: Randomised controlled trial intercostal catheter insertion (any reason) Peto odds ratio forest plot (refer to Figure 3.4)

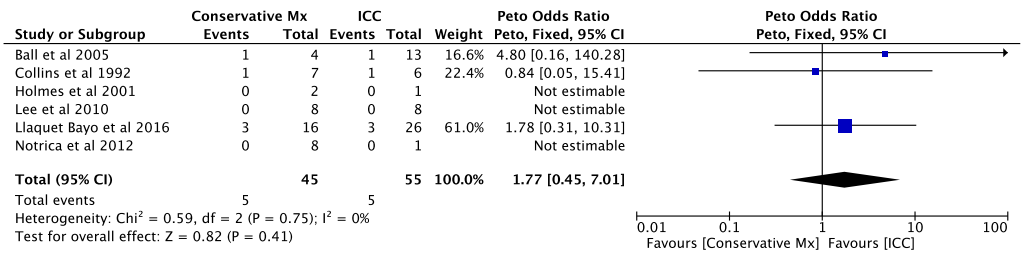


Figure 7.8: Cohort study intercostal catheter insertion (any reason) M-H forest plot (refer to Figure 3.5)

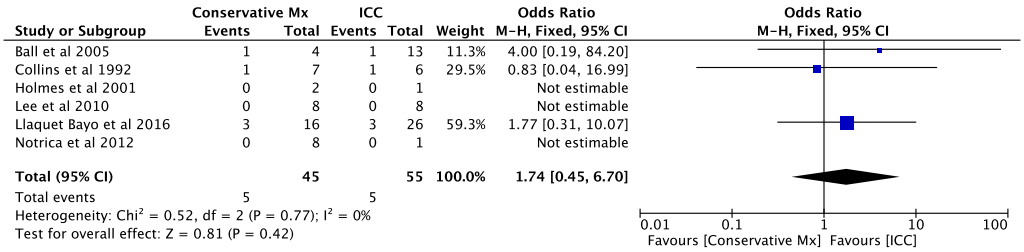


Figure 7.9: Cohort study intercostal catheter insertion (any reason) Peto odds ratio forest plot (refer to Figure 3.5)

7.1.3 Incidence of pneumonia/empyema

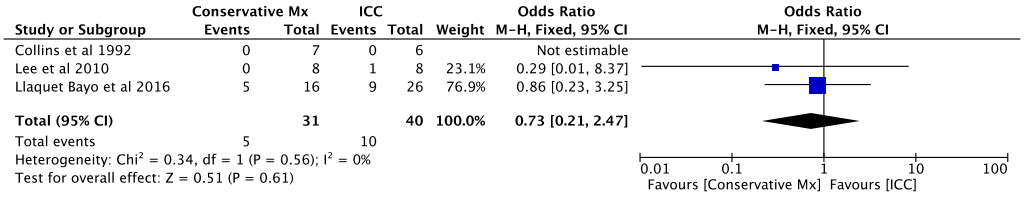


Figure 7.10: Cohort study incidence of pneumonia/empyema M-H forest plot (refer to Figure 3.6)

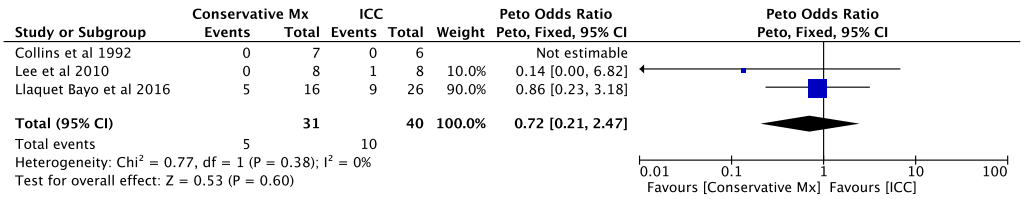


Figure 7.11: Cohort study incidence of pneumonia/empyema Peto odds ratio forest plot (refer to Figure 3.6)

7.2 Secondary outcomes

7.2.1 Mortality

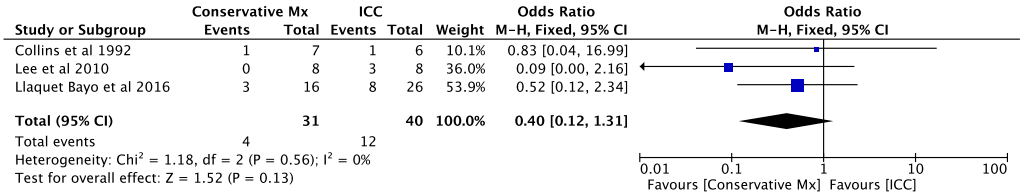


Figure 7.12: Cohort study mortality M-H forest plot (refer to Figure 3.7)

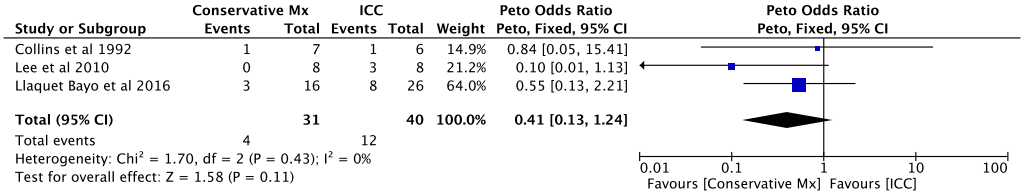


Figure 7.13: Cohort study mortality Peto odds ratio forest plot (refer to Figure 3.7)

7.2.2 Intercostal catheter insertion (progression to simple pneumothorax)

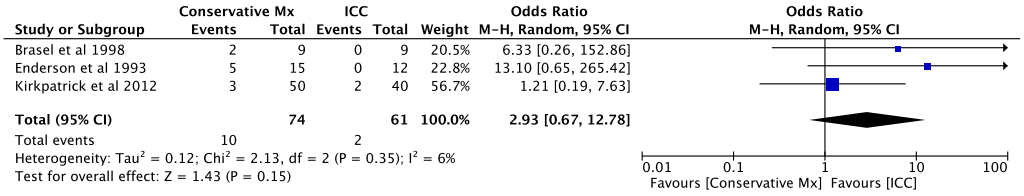


Figure 7.14: Randomised controlled trial intercostal catheter insertion (progression to simple pneumothorax) M-H forest plot (refer to Figure 3.8)

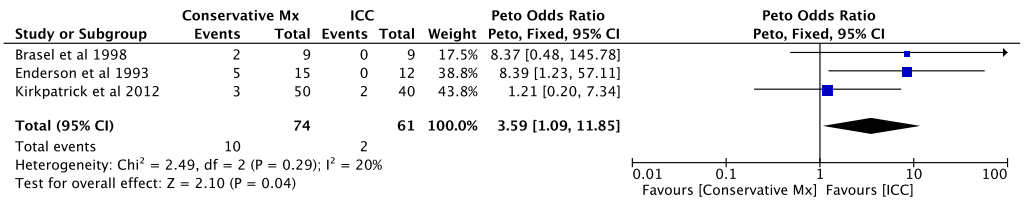


Figure 7.15: Randomised controlled trial intercostal catheter insertion (progression to simple pneumothorax) Peto odds ratio forest plot (refer to Figure 3.8)

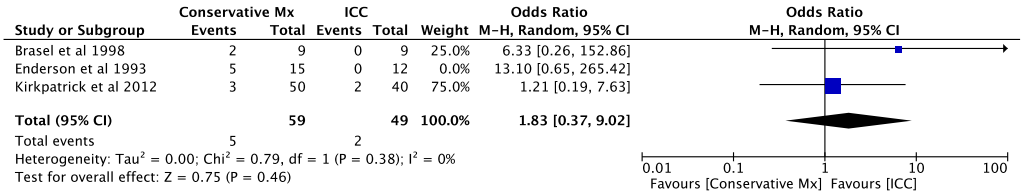


Figure 7.16: Randomised controlled trial intercostal catheter insertion (progression to simple pneumothorax) minus Enderson M-H forest plot (refer to Section 3.4.2.3)

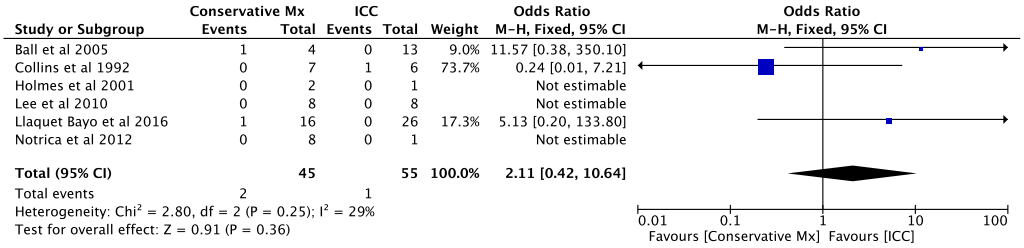


Figure 7.17: Cohort study intercostal catheter insertion (progression to simple pneumothorax) M-H forest plot (refer to Figure 3.9)

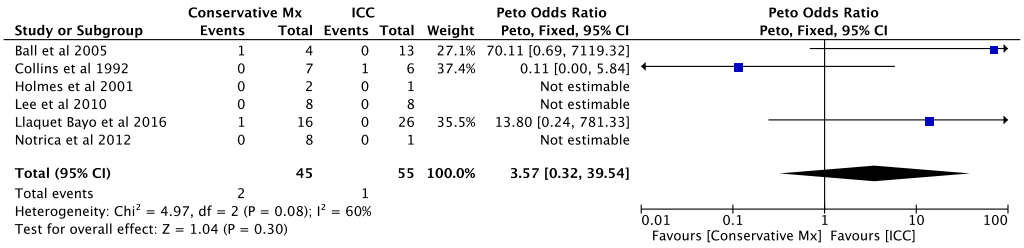


Figure 7.18: Cohort study intercostal catheter insertion (progression to simple pneumothorax) Peto odds ratio forest plot (refer to Figure 3.9)

7.2.3 Intercostal catheter insertion (non-pneumothorax reasons)

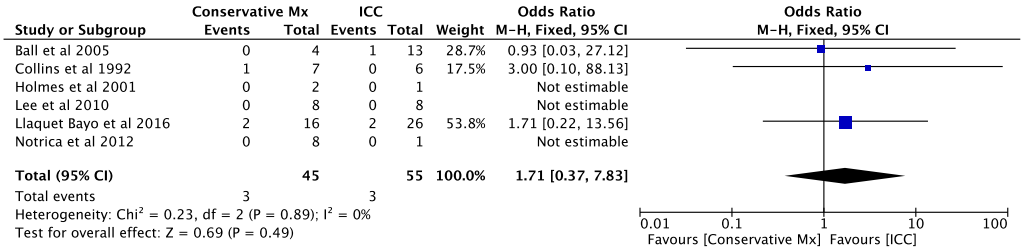


Figure 7.19: Cohort study intercostal catheter Insertion (non-pneumothorax reasons) M-H forest plot (refer to Figure 3.10)

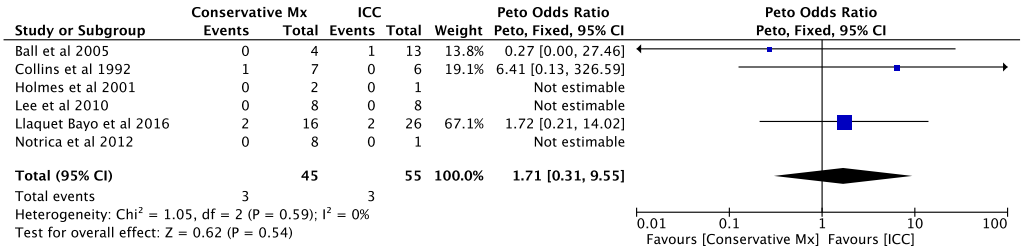


Figure 7.20: Cohort study intercostal catheter Insertion (non-pneumothorax reasons) Peto odds ratio forest plot (refer to Figure 3.10)

7.2.4 Intercostal catheter complications (composite)

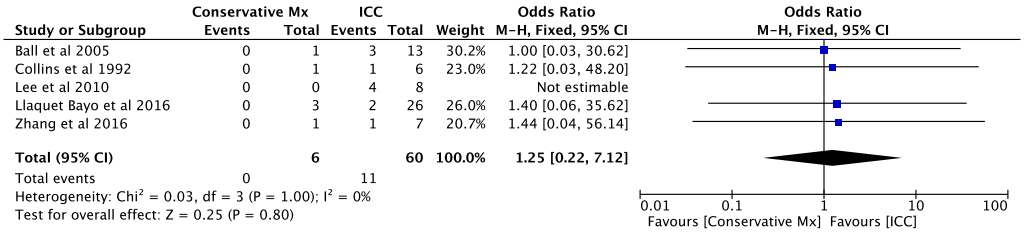


Figure 7.21: Cohort study intercostal catheter complication (composite) M-H forest plot (refer to Figure 3.11)

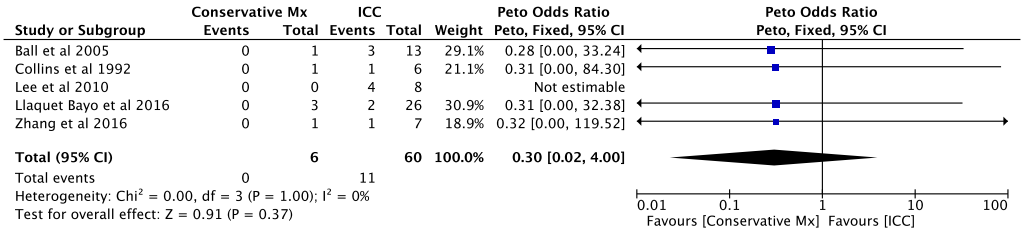


Figure 7.22: Cohort study intercostal catheter complication (composite) Peto odds ratio forest plot (refer to Figure 3.11)

References

1. Yadav K, Jalili M, Zehtabchi S. Management of Traumatic occult pneumothorax. Resuscitation. 2010; 81(9):1063-8.

2. Lesquen H, Avaro J, Gust L, Ford R, Beranger F, Natale C et al. Surgical Management for the first 48 h following blunt chest trauma: state of the art (excluding vascular injuries). Interactive Cardiovascular and Thoracic Surgery. 2015; 20(3): 399-408.

3. Drake R, Vogl W, Mitchell AWM. Gray's Anatomy for Students. Elsevier; 2005.

4. Lumb A. Nunn's Applied Respiratory Physiology. Elsevier; 7th ed, 2014.

5. Feller-Kopman D, Light R. Pleural Disease. New England Journal of Medicine. 2018; 378(8):740-51.

6. Light R. Pleural Diseases. Wolters-Kluwer; 2013.

7. Sharma A, Jindal P. Principles of diagnosis and management of traumatic pneumothorax. Journal of Emergencies, Trauma, and Shock. 2008; 1(1):34-41.

8. Ball C, Kirkpatrick A, Feliciano D. The Occult Pneumothorax: What have we learned? Canadian Journal of Surgery. 2009; 52(5):173-9.

9. Omar H, Abdelmalak H, Mangar D, Rashad R, Helal E, Camporesi E. Occult pneumothorax, revisited. Journal of Trauma. 2010; 4(12):1-6.

10. Zhang M, Teo L, Goh M, Go K. Occult pneumothorax in blunt trauma: is there a need for tube thoracostomy? European Journal of Trauma and Emergency Surgery. 2016; 42(6):785-90.

11. Wall S, Federle M, Jeffrey B, Brett C. CT Diagnosis of Unsuspeted Pneumothorax after Blunt Abdominal Trauma. American Journal of Roentgenology and Radium Therapy. 1983; 141(5):919-21.

12. Tocino I, Miller M, Frederick P, Thomas F. CT Detection of Occult Pneumothorax in Head Trauma. American Journal of Roentgenology and Radium Therapy. 1984; 143(5):987-90.

13. Kirkpatrick A, Sirois M, Laupland K, Liu D, Rowan K, Ball C, et al. Hand-Held Thoracic Sonography for Detecting Post-Traumatic Pneumothoraces: The Extended Focused Assessment With Sonography For Trauma (EFAST). Journal of Trauma. 2004; 57(2):288-95.

14. Ianniello S, Di Gaicomo V, Sessa B, Vittoria M. First-line sonographic diagnosis of pneumothorax in major trauma: accuracy of e-FAST and comparison with multidetector computed tomography. La Radologia Medica. 2013; 119(9):674-80.

15. Charbit J, Millet I, Maury C, Conte B, Roustan J, Taourel P et al. Prevalence of large and occult pneumothoraces in patients with severe blunt trauma upon hospital admission: experience of 526 cases in a French level 1 trauma center. American Journal of Emergency Medicine. 2015; 33(6):796-801.

16. Lee KL, Graham CA, Yeung JHH, Ahuja AT, Rainer TH. Occult pneumothorax in Chinese patients with significant blunt chest trauma: Incidence and management. Injury. 2010; 41(5):492-4.

17. Plurad D, Green D, Demetriades D, Rhee P. The Increasing Use of Chest Computed Tomography for Trauma: Is it Being overutilized? The Journal of trauma. 2007; 62(3):631-5.

18. Lell M, Wildeberger J, Alkadhi H, Damilakis J, Kachelriess M. Evolution in Computed Tomography: The Battle for Speed and Dose. Investigative Radiology 2015; 50(9):629-44.

19. Rubin G. Computed Tomography: Revolutionzing the Practice of Medicine for 40 Years. Radiology. 2014; 273(2 Suppl):S45-74.

20. Wagner P, Shah P. Airways and Alveoli. In: Firth J, Conlon C, Cox T, editors. Oxford Textbook of Medcine. 6th ed. Oxford University Press; 2020.

21. Gilmartin J, Wright A, Gibson G. Effects of pneumothorax or pleural effusion on pulmonary function. Thorax. 1985; 40(1):60-5.

22. Kilburn K. Cardiorespiratoy effects of large pneumothorax in conscious and anesthetized dogs. Journal of Applied Physiology. 1963; 18(2):279-83.

23. Norris R, Jones J, Bishop J. Respiratory gas exchange in patients with spontaneous pneumothorax. Thorax. 1968; 23(4):427-33.

24. Moran J, Jones R, Wolfe W. Regional pulmonary function during experimental unilateral pneumothorax in the awake state. Journal of Thoracic Surgery. 1977; 74(3):396-402.

25. Anthonisen N. Regional Lung Function in Spontaneous Pneumothorax. American Review of Respiratory Disease. 1977; 115(5):873-6.

26. Leigh-Smith S, Harris T. Tension Pneumothorax - time for a re-think? Emergency Medicine Journal. 2005; 22(1):8-16.

27. Roberts DJ, Leigh-Smith S, Faris P, Blackmore C, C B, Robertson H, et al. Clinical Presentation of Patients with Tension Pneumothorax: A Systematic Review. Annals of Surgery. 2015; 261(6):1068-78.

28. Nelson D, Porta C, Satterly S, Blair K, Johnson E, Inaba K, et al. Physiology and cardiovasular effect of severe tension pneumothorax in a porcine model. Journal of Surgical Research. 2013; 184(1):450-7.

29. Rutherford R, Hurt H, R B, Tubb J. The pathophysiology of progression, tension pneumothorax. Journal of Trauma. 1968; 8(2):212-27.

30. Bitto T, Mannion J, Stephenson L, Hammond R, Lanken P, Miller W, et al. Pneumothorax during positive-pressure mechanical ventilation. Journal of Thoracic and Cardiovascular Surgery. 1985; 89(4):585-91.

31. Simmons D, Hemingway A, Richiuti N. Acute Circulatory Effects of Pneumothorax in Dogs. Journal of Applied Physiology. 1958; 12(2):255-61.

32. Carvalho P, Hildebrandet J, Charan N. Changes in bronchial and pulmonary arterial blood flow with progressive tension pneumothorax. Journal of Applied Physiology. 1996; 81(4):1664-9.

33. Beards S, Lipman J. Decreased cardiac index as an indicator of tension pneumothorax in the ventilated patient. Anaesthesia. 1994; 49(2):137-41.

34. Emergency Trauma Management. Emergency Trauma Management Course. [internet]. [cited 4th March 2019]. Available from: https://etmcourse.com

35. American College of Surgeons. Advanced Trauma Life Support Student Course Manual. 10th ed. Chicargo, USA: Committee on Trauma; 2018.

36. Chapman S, Robinson G, Stradling J, West S, Wrightson J. Pneumothorax. Oxford Handbook of Respiratory Medicine. Oxford University Press; 2009.

37. Kinnear W. Pneumothorax. Topics in Respiratory Medicine. CRC Press LLC; 1998.

38. Anzeuto A, Frutos-Vivar F, Esteban A, Alia I, Brochard L, Stewart T, et al. Incidence, risk facotrs and outcome of barotrauma in mechanically ventilated patients. Intensive Care Medicine. 2004; 30(4):612-9.

39. Milisavljevic S, Spasic M, Arsenijevic M. Thoracic Trauma. In: Cagani L, editor. Current concepts in general thoracic surgery. Rijeka, Croatia: Oliver Kurelic; 2012; p. 198-297.

40. O'Connor A, Morgan W. Radiological review of pneumothorax. British Medical Journal. 2005; 330(7506):1493-7.

41. Neff M, Monk J, Peters K, Nikhilesh A. Detection of Occult Pneumothoraces on Abdominal Computed Tomographic Scans in Trauma Patients. Journal of Trauma. 2000; 49(2):281-5.

42. Ball C, Kirkpatrick A, Fox D, Laupland K, Louis L, Andrews G, et al. Are Occult Pneumothoraces Truly Occult or Simply Missed? Journal of Trauma - Injury, Infection and Critical Care. 2006; 60(2):294-9.

43. Tseng Y-H, Liu K-L, Shih I-L. Deep Sulcus Sign. Emergency Medicine Journal. 2012; 29(7):608.

44. Sur B, Wandtke J, Hobbs S. Pneumothorax: How to Recognize Subtle Signs and Avoid Pitfalls. Contemporay Diagnostic Radiology. 2015; 38(4):1-8.

45. Rierson D, Bueno J. Pneumothorax in the Supine Patient: Subtle Radiographic Signs. Journal of Thoracic Imaging. 2016; 31(4):W16-W22.

46. Ball C, Kirkpatrick A, Laupland K, Fox D, Litvinchuk S, Dyer D, et al. Factors related to the failure of radiographic recognition of occult post traumatic pneumothoraces. The American Journal of Surgery. 2005; 189(5):541-6.

47. Kaufman C, Bokhari J. The floating cardiac fat pad - sign of occult pneumothorax. Emergency Radiology. 2016; 23(4):417-9.

48. Brar M, Bains I, Brunet G, Nicolaou S, Ball C, Kirkpatrick A. Occult Pneumothoraces Truly Occult or Simply Missed: Redux. Journal of Trauma - Injury, Infection and Critical Care. 2010; 69(6):1335-7.

49. Primack S, Collins J. Blunt nonaortic chest trauma: radiographic and CT findings. Emergency Radiology. 2002; 9:5-12.

50. Lichtenstein D, Menu Y. A bedside ultrasound sign ruling out pneumothorax in the critically ill: lung sliding. Chest. 1995; 108(5):1345-8.

51. Husain L, Hagopian L, Wayman D, Baker W, Carmody K. Sonographic diagnosis of pneumothorax. Journal of Emergencies, Trauma, and Shock. 2012; 5(1):76-81.

52. Lichtenstein D, Meziere G, Lascols N, Biderman P, Courret J-P, Gepner A, et al. Ultrasound Diagnosis of occult pneumothorax. Critical Care Medicine. 2005; 33(6):1231-8.

53. Lichtenstein D. Lung ultrasound in the critically ill. Annals of Intensive Care. 2014; 4(1):1.

54. Lichtenstein D, Meziere G, Biderman P, Gepner A. The “lung point”: an ultrasound sign specific to pneumothorax. Intensive Care Medicine. 2000; 26(10):1434-40.

55. Solidati G, Testa A, Sher S, Pignataro G, La Sala M, Silveri N. Occult Traumatic Pneumothorax: Diagnostic Accuracy of Lung Ultrasonography in the Emergency Department. Chest. 2008; 133(1):204-11.

56. Retief J, Chopra M. Pitfalls in the ultrasonographic diagnosis of pneumothorax. Journal of the Intensive Care Society 2017; 18(2):143-5.

57. Ouellet J, Ball C, Panebianco N, Kirkpatrick A. The sonographic diagnosis of pneumothorax. Journal of Emergencies, Trauma, and Shock. 2011; 4(4):504-7.

58. Matsumoto S, Sekine K, Funabiki T, Orita T, Shimizu M, Hayashida K, et al. Diagnositic accuracy of oblique chest radiograph for occult pneumothorax: comparison with ultrasonography. World Journal of Emergency Surgery. 2016; 11:5.

59. Wilkerson R, Stone M. Sensitivity of Bedside Ultrasound and Supine Anteroposterior Chest Radiographs for the Identification ofo Pneumothorax After Blunt Trauma. Academic Emergency Medicine. 2010; 17(1):11-7.

60. Kirkpatrick A, Gillman L, Chun R, Ball C, Tiruta C, Lall R, et al. Opening Pandora's box: the potential benefit of the expanded FAST exam is partially congounded by the unknows regarding the significance of the occult pneumothorax. Critical Ultrasound Journal. 2010; 1:117-22.

61. American College of Surgeons. Advanced Trauma Life Support Student Course Manual. 9th ed. Chicargo, USA: Committee on Trauma; 2012.

62. Hudson A. Traumatic occult pneumothorax - A UK perspective. Resuscitation. 2011; 82(5):639.

63. Enderson B, Abdalla R, Frame S, Casey M, Gould H, Maull L. Tube Thoracostomy for Occult Pneumothorax: A Prospective Randomized Study of it Use. Journal of Trauma. 1993; 35(5):726-30.

64. Moore FO, Goslar PW, Coimbra R, Velmahos G, Brown CVR, Coopwood TB, et al. Blunt traumatic occult pneumothorax: Is observation safe?-results of a prospective, AAST multicenter study. Journal of Trauma - Injury, Infection and Critical Care. 2011; 70(5):1019-25.

65. Kirkpatrick AW, Rizoli S, Ouellet J-F, Roberts DJ, Sirois M, Ball CG, et al. Occult pneumothoraces in critical care: A prospective multicenter randomized controlled trial of pleural drainage for mechanically ventilated trauma patients with occult pneumothoraces. Journal of Trauma and Acute Care Surgery. 2013; 74(3):747-54.

66. Steven W, Etoch MD, Marcos F, Bar-Natan MD, Frank B, Miller MD . Tube Thoracostomy: Factors Related to Complications. Archives of Surgery. 1995; 130(5):521-6.

67. McConaghy P, Kennedy N. Tension Pneumothorax due to Intrapulmonary Placement of Intercostal Drain. Anaesthesia and Intensive Care. 1995; 23:496-8.

68. Walcott-Sapp S, Sukumar M. 2015. A History of Thoracic Drainage: From Ancient Greeks to Wound Sucking Drummers to Digital Monitoring. [internet]. [cited 25th April

2020]. Available from https://www.ctsnet.org/article/history-thoracic-drainage-ancient-greeks-wound-sucking-drummers-digital-monitoring

69. Laws D, Neville E, Duffy J. BTS guidelines for the insertion of a chest drain. Thorax. 2003; 58(Suppl II):ii53-9.

70. Havelock T, Teoh R, Laws D, Gleeson F. Pleural procedures and thoracic ultrasound: British Thoracic Society pleural disease guideline 2010. Thorax. 2010; 65(Suppl 2):ii61-ii76.

71. McElnay P, Lim E. Modern Techniques to Insert Chest Drains. Thoracic Surgery Clinics. 2017; 27(1):29-34.

72. Elsayed H, Roberts R, Emadi M, Whittle I, Shackcloth M. Chest Drain insertion is not a harmless procedure - are we doing it safely? Interactive Cardiovascular and Thoracic Surgery 2010; 11(6):745-9.

73. Dev S, Nascimiento B, Simone C, Chien V. Chest-Tube Insertion. New England Journal of Medicine. 2007; 357:e15.

74. Wraight W, Tweedie D, Parkin I. Neurovascular anatomy and variation in the fourth, fifth and sixth intercostal spaces in the mid-axillary line: a cadaveric study in respect of chest drain insertion. Clinical Anatomy. 2005; 18(5):346-9.

75. Seldinger S. Catheter Replacement of the Needle in Percutaneous Arteirography: A new technique. Acta Radiologica. 1953; 39(5):368-76.

76. ACI Respiratory Network. Pleural Drains in Adults - consensus guideline. 2016 [internet]. [cited 5th April 2019]. Available from: https://www.aci.health.nsw.gov.au/__data/assets/pdf_file/0018/201906/PleuralDrains_Guideline-021116.pdf

77. Porcel J. Chest Tube Drainage of the Pleural Space: A Concise Review for Pulmonologists. Tubeculosis & Respiratory Disease. 2017; 81(2):106-15.

78. Kulvatunjou N, Erickson L, Vijayasekaran A, Gries L, Friese J, O'Keeffe T, et al. Randomized clinical trial of pigtail catheter versus chest tube in injured patients with uncomplicated traumatic pneumothorax. British Journal of Surgery. 2014; 101(2):17-22.

79. Gilbert T, McGrath B, Soberman M. Chest Tubes: Indications, Placement, Management and Complications. Journal of Intensive Care Medicine. 1993; 8(2):73-86.

80. Deneuville M. Morbidity of percutaneous tube thoracostomy in trauma patients. European Journal of Cardiothoracic Surgery. 2002; 22(2):673-8.

81. Heimlich H. A Flutter Valve to Replace Underwater Drainage Bottles. JAMA. 1965; 192(3):262.

82. Gogakos A, Barbetakis N, Lazaridis G, Papaiwannou A, Karavergou A, Lampaki S, et al. Heimlich valve and pneumothorax. Annals of Translational Medicine. 2015; 3(4):54.

83. Kam A, O'Brien M, Kam P. Pleural Drainage Systems. Anaesthesia 1993; 48(2):154-61.

84. Zisis C, Tsirgogianni K, Lazaridis G, Lampaki S, Baka S, Mpoukovinas I, et al. Chest Drainage Systems in Use. Annals of Translational Medicine. 2015; 3(3):43.

85. Sethuraman K, Duong D, Mehta S, Director T, Crawford D, St. George J, et al. Complications of tube thoracostomy placement in the emergency department. The Journal of Emergency Medicine. 2008; 40(1):14-20.

86. Bailey R. Complications of tube thoracostomy in trauma. Journal of Accident and Emergency Medicine. 2000; 17(2):111-4.

87. Ball C, Lord J, Laupland K, Gmora S, Mulloy R, Schieman C, et al. Chest Drain Complications: How well are we training our residents? Canadian Journal of Surgery. 2007; 50(6):450-8.

88. Hernandez M, Khatib M, Prokop L, Zielinski M, Aho J. Complications in Tube Thoracostomy: Systematic review and Meta-analysis. Journal of Trauma and Acute Care Surgery. 2018; 85(2):410-6.

89. Alrahbi R, Easton R, Bendinelli C, Ennninghorst N, Sisak K, Balogh Z. Intercostal catheter insertion: are we really doing well? ANZ Journal of Surgery. 2012; 82(392-394).

90. Kashani P, Shirafkan A, Amirbeigl A, Hatamabadt H. Comparing the Quality and Complications of Tube Thoracsotomy by Emergency Medicine and Surgery Residents; a Cohort Study. Emergency 2017; 5(1):e33.

91. Kesieme E, Dongo A, Ezemba N, Irekpita E, Jebbin N, Kesieme C. Tube Thoracostomy: Complications and Its Management. Pulmonary Medicine. 2012; 2012: Article ID 256878.

92. Dural K, Gulbahar G, Kocer B, Sakinci U. A novel and safe technique in closed tube thoracostomy. Journal of Cardiothoracic Surgery. 2010; 5:21.

93. John M, Razi S, Sainathan S, Stavropoulos C. Is the trocar technique for the tube thoracostomy safe in the current era? Interactive Cardiovascular and Thoracic Surgery. 2014; 19(1):125-8.

94. Kong V, Clarke D. The Spectrum of Visceral Injuries Secondary to Misplaced Intercostal Chest Drains: Experience from a high volume trauma service in South Africa. Injury. 2014; 45(9):1435-9.

95. Menger R, Telford G, Kim P, Bergey M, Foreman J, Sarani B, et al. Complications following thoracic trauma managed with tube thoracostomy. Injury. 2012; 43(1):46-50.

96. Gerard P, Kaldawi E, Litani V, Lenora R, Tessler S. Right-sided pneumothorax as a result of a left-sided chest tube. Chest. 1993; 103(5):1602-3.

97. Baldt M, Bankier A, Germann P, Poschl G, Skrbensky G, Herold C. Complications after emergency tube thoracostomy: assessment with CT. Radiology 1995; 195(2):539-43.

98. Lim K, Tai S, Chan C, Hsu Y, Hsu W, Lin B, et al. Diagnosis of malpositioned chest tubes after emergency tube thoracostomy: is computed tomography more accurate than chest radiography? Clinicaly Imaging. 2005; 29(6):401-5.

99. Kwiatt M, Tarbox A, Seamon M, Swaroop M, Cipolla J, Allen C. Thoracostomy tubes: a comprehensive review of complications and related topics. International Journal of Critical Illness and Injury Science. 2014; 4(2):143-55.

100. Mao M, Hughes R, Papadimos T, Stawicki S. Complications of Chest Tubes: a focused clinical synopsis. Current Opinion in Pulmonary Medicine. 2015; 21(4):376-86.

101. Kollef M, Dothager D. Reversible cardiogenic shock due to chest tube compression of the right ventricle. Chest. 1991; 99(5):976-80.

102. Echevarria C, Twomey D, Dunning J, Chanda B. Does re-expansion pulmonary oedema exist? Interactive Cardiovascular and Thoracic Surgery. 2008; 7(3):485-9.

103. Helling T, Gyles N, Eisenstein V, Soracco C. Complications Following Blunt and Penetrating Injuries in 216 Victims of Chest Trauma Requiring Tube Thoracostomy. Journal of Trauma. 1989; 29(10):1367-70.

104. Eren S, Esme H, Sehitogullari A, Durkan A. The risk factors and management of posttraumatic empyema in trauma patients. Injury. 2008; 39(1):44-9.

105. Del Pilar Quiroga M, Charry J, Becerra N, Garcia J, Munoz K, Lara R. Developing risk factors for post traumatic empyema in patients with chest trauma. Journal of Acute Disease. 2015; 4(1):48-50.

106. Davies H, Merchant S, McGown A. A Study of the complications of small bore 'Seldinger' intercotal chest drains. Respirology. 2008; 13(4):603-7.

107. Anand R, Whelan J, Ferrada P, Duane T, Malhotra A, Aboutanos M, et al. Thin Chest Wall is an Independent Risk Factor for the Development of Pneumothorax after Chest Tube Removal. The American Surgeon. 2012; 78(4):478-80.

108. Chadwick A, Halfard R, Ali M. Intercostal chest drains: Are you confident going on the pull? If not use the I-T-U approach. Journal of Intensive Care Society. 2015; 16(4):312-5.

109. Novoa N, Jimenez M, Varela G. When to Remove a Chest Tube. Thoracic Surgery Clinics. 2017; 27(1):41-6.

110. French D, Dilena M, LaPlante S, Shamji F, Sundaresan S, Villeneuve J, et al. Optimizing postoperative care protocols in thoracic surgery: best evidence and new technology. Journal of Thoracic Disease. 2015; 8(Suppl 1):S3-11.

111. Paydar S, Ghahramani Z, Johari H, Khezri S, Ziaeian B, Ghayyoumi M, et al. Tube Thoracostomy (Chest Tube) Removal in Traumatic Patients: What Do We Know? What Can We Do? Bulletin of Emergency and Trauma. 2015; 3(2):37-40.

112. Bell R, Ovadia P, Abdullah F, Spector S, Rabinovici R. Chest Tube Removal: End-Inspiration or End-expiration? Journal of Trauma. 2001; 50(4):674-7.

113. Cerfolio R, Bryant A, Skylizard L, Minnich D. Optimal technique for the removal of chest tubes after pulmonary resection. Journal of Thoracic and Cardiovascular Surgery. 2013; 145(6):1535-9.

114. Shoemaker W, Velmahos G, Demetriades D. Procedures and Monitoring for the Critically Ill. Saunders; 1st ed, 2001.

115. Macintyre N. Mechanical Ventilation. In: Broaddus C, Mason R, Ernst J, King Jr T, Lazarus S, Murray J, et al., editors. Murray & Nadel's Textbook of Respiratory Medicine. 6th ed. Philadelphia, USA: Saunders, Elsevier 2016.

116. Munoz Bonet J. Definitions in Mechanical Ventilation Annals of Pediatria. 2003; 59(1):60-6.

117. Bersten A. Mechanical Ventilator Support. In: Bersten A, Handy J, editors. Oh's Intensive Care Manual. 8th ed. Elsevier; 2019.

118. Hyzy R, McSparron J. Overview of initiating invasive mechanical ventilation in adults in the intensive care unit. UpToDate; 2020 [internet]. [updated April 2020; cited 14th May 2020]. Available from: https://www.uptodate.com/contents/overview-of-initiating-invasive-mechanical-ventilation-in-adults-in-the-intensive-care-unit

119. Grinnan D, Truwit J. Clinical Review: Respiratory mechanics in spontaneous and assisted ventilation. Critical Care. 2005; 9(5):472-84.

120. Soni N, Williams P. Positive pressure ventilation: what is the real cost? British Journal of Anaesthesia. 2008; 101(4):446-57.

121. Huang Y, Singh J. Basic Modes of Mechanical Ventilation In: Papadakos P, Lachman B, editors. Mechanical Ventilation: Clinical Applications and Pathophysiology. Elsevier; 2008.

122. The Acute Respiratory Distress Syndrome Network. Ventilation with Lower Tidal Volumes as Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome. New England Journal of Medicine. 2000; 342(18):1301-8.

123. Petrucci N, De Feo C. Lung protective ventilation strategy for the acute respiratory distress syndrome. Cochrane Database of Systematic Reviews. 2013; (2):CD003844.

124. Checkley W, Brower R, Korpak A, Thompson B, Acute Respiratory Distress Syndrome Network Invesitgators. Effects of a Clinical Trail on Mechanical Ventilation Practices in Patients with Acute Lung Injury. American Journal of Repiratory and Critical Care Medicine. 2008; 177(11):1215-22.

125. Esteban A, Ferguson N, Meade M, Frutos-Vivar F, Apeztegiua C, Brochard L, et al. Evolution of Mechanical Ventilation in Response to Clinical Research. American Journal of Repiratory and Critical Care Medicine. 2008; 177(2):170-7.

126. Gu W-J, Wang F, Liu J-C. Effect of lung-protective ventilation with lower tidal volumes on clinical outcomes among patients undergoing surgery: a meta-analysis of randomized controlled trials. Canadian Medical Association Journal. 2015; 187(3):E101-9.

127. Neto A, Cardoso S, Manetta J, Pereira V, Esposito D, Pasqualucci M, et al. Association Between Use of Lung-Protective Ventilation with Lower Ridal Volumes and Clinical Outcomes Among Patients Without Acute Respiratory Distress Syndrome: A Meta-analysis. Journal of the American Medical Association. 2012; 308(16):1651-9.

128. Weingart S. Managing Initial Mechanical Ventilation in the Emergency Department. Annals of Emergency Medicine. 2016; 68(5):614-617.

129. Santamaria J, Tobin A, Reid D. Do we practice low tidal-volume ventilation in the intensive care unit? A 14-year audit. Critical Care and Resuscitation 2015; 17(2):108-12.

130. Lipes J, Bojmehrani A, Lellouche F. Low Tidal Volume Ventilation in Patients without Acute Respiratory Distress Syndrome: A Paradigm Shift in Mechanical Ventilation. Critical Care Research and Practice. 2012:416862.

131. Pinhu L, Whitehead T, Evans T, Griffiths M. Ventilator-associated lung injury. Lancet. 2003; 361(9354):332-40.

132. Chastre J, Fago J-Y. State of the Art: Ventilator-associated Pneumonia. American Journal of Repiratory and Critical Care Medicine. 2002; 165(7):867-903.

133. Diaz R, Heller D. Barotrauma and Mechanical Ventilation. In: StatPearls [Internet]. Treasure Island, Florida: StatPearls Publishing; 2020. [cited 22nd May 2020]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK545226

134. Sandur S, Stoller J. Pulmonary complications of mechanical ventilation. Clinics in Chest Medicine. 1999; 20(2):223-46.

135. Hyzy R, Slutsky A. Ventilator-induced lung injury. UpToDate; 2020 [internet]. [updated April 2020; cited 22nd May 2020]. Available from: https://www.uptodate.com/contents/ventilator-induced-lung-injury

136. Malhotra A, Schwartzstein R. Pulmonary consequences of supplemental oxygen. UpToDate; 2020 [internet]. [updated April 2020; cited 22nd May 2020]. Available from: https://www.uptodate.com/contents/pulmonary-consequences-of-supplemental-oxygen

137. Balk E, Bonis P. Systematic review and meta-analysis. UpToDate; 2020 [internet]. [updated April 2020; cited 22nd May 2020]. Available from: https://www.uptodate.com/contents/systematic-review-and-meta-analysis

138. Aromataris E, Riitano D. Constructing a Search Strategy and Searching for Evidence: A guide to the literature search for a systematic review. Australian Journal of Nursing. 2014; 114(5):49-55.

139. OCEBM Levels of Evidence Working Group. The Oxford 2011 Levels of Evidence. Oxford Centre for Evidence-Based Medicine [internet]. [cited 21st May 2020]. Available from: http://www.cebm.net/wp-content/uploads/2014/06/CEBM-Levels-of-Evidence-2.1.pdf

140. National Health and Medical Research Council. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines: Stage 2 Consultation. Canberra, Australia 2009. [internet]. [cited 19th May 2020]. Available from https://www.mja.com.au/sites/default/files/NHMRC.levels.of.evidence.2008-09.pdf

141. Crowther M, Lim W, Crowther M. Systematic review and meta-analysis methodology. Blood. 2010; 116(17):3140-6.

142. Khan K, Kunz R, Kleijnen J, Antes G. Five steps to conducting a systematic review. Journal of the Royal Society of Medicine. 2003; 96(3):118-21.

143. Tufanaru C, Munn Z, Aromataris E, Campbell J, Hopp L. Chapter 3: Systematic reviews of effectiveness. In: Aromataris E, Munn Z (Editors). JBI Manual for Evidence Synthesis. JBI,

2020. [internet]. [cited 13th April 2019]. Available from: https://synthesismanual.jbi.global. https://doi.org/10.46658/JBIMES-20-04

144. Higgins J, Thomas J, Chandler J, Cumpston M, Li T, Page M, et al. Cochrane Handbook for Systematic Reviews of Interventions. Cochrane; 2019 [internet]. [cited 22nd May 2020]. Available from: www.training.cochrane.org/handbook

145. Moher D, Liberati A, Tetzlaff J, Altman D, The PRISMA Group. Preferred Reporting Items for Systemeatic Reviews and Meta-Analyses: The PRISMA Statement. BMJ. 2009; 339:b2535.

146. Smith JA, Secombe P, Aromataris E. Effectiveness and Safety of conservative management of occult pneumothorax in mechanically ventilated patients: a systematic review protocol. JBI Database of Systematic Reviews and Implemention Reports. 2019; 17(0):1-9.

147. Lau J, Ionnidis J, Schmid C. Quantitative Synthesis in Systematic Reviews. Annals of Internal Medicine. 1997; 127(9):820-6.

148. National Health and Medical Research Council. How to review the evidence: systematic identification and review of the scientific literature. Canberra, Australia: Commonwealth of Australia, 1st ed, 2000.

149. Aromataris E, Hopp L, Munn Z. Synthesizing Evidence of Risk. Philadephia, USA: Wolters Kluwer, 1st ed, 2011

150. Golder S, Loke Y, Bland M. Meta-analysis of Adverse Effects Data Derived from Randomised Controlled Trials as Compared to Observational Studies: Methodological Overview. PLoS Medicine. 2011; 8(5):e1001026.

151. Ahlers S, Van Der Veen A, Van Dijk M, Tibboel D, Knibbe C. The Use of the Behavioural Pain Scale to Assess Pain in Concious Sedated Patients. Anesthesia and Analgesia. 2010; 110(1):127-33.

152. Rijkenberg S, Stilma W, Endeman H, Bosma R, Vann Straaten O. Pain measurement in mechanially ventilated critically ill patients: Behavioral Pain Scale versus Critical-Care Pain Observation Tool. Journal of Critical Care. 2015; 30(1):167-72.

153. ANZCA Faculty of Pain Medicine. Opioid Dose Equivalence. [internet]. [cited 14th April 2019]. Available from: https://www.anzca.edu.au/getattachment/6892fb13-47fc-446b-a7a2-11cdfe1c9902/PM01-(Appendix-2)-Opioid-Dose-Equivalence-Calculation-of-Oral-Morphine-Equivalent-Daily-Dose-(oMEDD).aspx

154. Clariative Analytics. Endnote X8.2. Philadelphia, USA 2016.

155. JBI. The System for the Unfifed Management, Assessment and Review of Information (SUMARI). 2017 [internet]. [cited March 7 2019]. Available from: https://www.jbisumari.org

156. Herbison P, Hay-Smith J, Gillespie W. Adjustment of meta-analyses on the basis of quality scores should be abandoned. Journal of Clinical Epidemiology 2006; 59(12):1249-56.

157. Bradburn M, Deeks J, Berlin J, Localio R. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. Statistics in Medicine. 2007; 26(1):53-77.

158. Sweeting M, Sutton A, Lambert P. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Statistics in Medicine. 2004; 23(9):1351-75.

159. Efthimiou O. Practical guide to the meta-analysis of rare events. Evidence Based Mental Health. 2018; 21(2):72-6.

160. StataCorp. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC; 2017.

161. Simmonds M, Higgins J. A general framework for the use of logistic regression models in meta-analysis. Statistical Methods in Medical Research. 2014; 25(6):2858-77.

162. Chang B-H, Hoaglin D. Meta-analysis of Odds Ratios: Current Good Practices. Medical Care. 2017; 55(4):328-35.

163. Lane P. Meta-analysis of incidence of rare events. Statistical Methods in Medical Research. 2011; 22(2):117-32.

164. Abo-Zaid G, Guo B, Deeks J, Debray T, Steyerberg E, Moons K, et al. Individual participant data meta-analysis should not ignore clustering. Journal of Clinical Epidemiology. 2013; 66(8):865-73.

165. Review Manager (RevMan) [Computer Program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration 2014.

166. Lau J, Loannidis J, Terrin N, Schmid C, Olkin I. The Case of the Misleading Funnel Plot. British Medical Journal. 2006; 333(7568):597-600.

167. Fulton C, Bratu I. Occult pneumothoraces in ventilated pediatric trauma patients: a review. Canadian Journal of Surgery. 2015; 58(3):177-80.

168. University of Calgary, CHU de Quebec-Universite Laval, Sunnybrook Health Sciences Centre, Canadian Intensive Care Foundation, London Health Sciences Centre. Management of Occult Pneumothoraces in Mechanically Ventilated Patients. [internet]. [Cited 15th August 2019]. Available from: https://ClinicalTrials.gov/show/NCT00530725; 2006.

169. Collins J, Levine G, Waxman K. Occult Traumatic Pneumothorax: Immediate Tube Thoracostomy Versus Expectant Management. The American Surgeon. 1992; 58(12):743-6.

170. Ball C, Kirkpatrick A, Laupland K, Fox D, Nicolaou S, Anderson I, et al. Incidence, Risk Factor, and Outcomes for Occult Pneumothoraces in Victims of Major Trauma. Journal of Trauma. 2005; 59(4):917-25.

171. Ouellet JF, Trottier V, Kmet L, Rizoli S, Laupland K, Ball CG, et al. The OPTICC trial: a multi-institutional study of occult pneumothoraces in critical care. American Journal of Surgery.. 2009; 197(5):581-6.

172. Kirkpatrick AW, Stephens Mv, Fabian T. Canadian Association of General Surgeons and American College of Surgeons Evidence Based Reviews in Surgery. 18 - Treatment of occult pneumothoraces from blunt trauma. Canadian Journal of Surgery. 2006; 49(5):358-61.

173. Barrios C, Tran T, Malinoski D, Lekawa M, Dolich M, Lush S, et al. Successful management of occult pneumothorax without tube thoracostomy despite positive pressure ventilation. The American Surgeon. 2008; 74(10):958-61.

174. Johnson G. Traumatic pneumothorax: is a chest drain always necessary? Journal of Accident and Emergency Medicine. 1996; 13(3):173-4.

175. Lamb ADG, Qadan M, Gray AJ. Detection of occult pneumothoraces in the significantly injured adult with blunt trauma. European Journal of Emergency Medicine. 2007; 14(2):65-7.

176. Kaiser M, Whealon M, Barrios C, Dobson S, Malinoski D, Dolich M, et al. The clinical significance of occult thoracic injury in blunt trauma patients. The American Surgeon. 2010; 76(10):1063-6.

177. Wolfman NT, Gilpin JW, Bechtold RE, Meredith JW, Ditesheim JA. Occult pneumothorax in patients with abdominal trauma: CT studies. Journal of Computer Assisted Tomography. 1993; 17(1):56-9.

178. Walker SP, Barratt SL, Thompson J, Maskell NA. Conservative Management in Traumatic Pneumothoraces An Observational Study. Chest. 2018; 153(4):946-53.

179. Brasel KJ, Stafford RE, Weigelt JA, Tenquist JE, Borgstrom DC. Treatment of occult pneumothoraces from blunt trauma. The Journal of Trauma. 1999; 46(6):987-90; discussion 90-1.

180. Schulz K, Altman D, Moher D. CONSORT 2010 Statement: updated guidelines for reportingn parallell group randomised trials. BMJ. 2010; 340:c332.

181. Holmes JF, Brant WE, Bogren HG, London KL, Kuppermann N. Prevalence and importance of pneumothoraces visualized on abdominal computed tomographic scan in children with blunt trauma. The Journal of Trauma. 2001; 50(3):516-20.

182. Llaquet Bayo H, Montmany Vioque S, Rebasa P, Navarro Soto S. Results of conservative treatment in patients with occult pneumothorax. Cirugia Espanola. 2016; 94(4):232-6.

183. Notrica DM, Garcia-Filion P, Moore FO, Goslar PW, Coimbra R, Velmahos G, et al. Management of pediatric occult pneumothorax in blunt trauma: A subgroup analysis of the American Association for the Surgery of Trauma multicenter prospective observational study. Journal of Pediatric Surgery. 2012; 47(3):467-72.

184. Wilson H, Ellsmere J, Tallon J, Kirkpatrick A, Wilson H, Ellsmere J, et al. Occult pneumothorax in the blunt trauma patient: tube thoracostomy or observation? Injury. 2009; 40(9):928-31.

185. Kulvatunjou N, Vijayasekaran A, Hansen A, Wynne J, O'Keeffe T, Friese R, et al. Two-Year Experience of Using Pigtail Catheters to Treat Traumatic Pneumothorax: A Changing Trend. Trauma. 2011; 71(5):1104-7.

186. Chang S-H, Kang Y-N, Chiu H-Y, Chiu Y-H. A Systematic Review and Meta-Analysis Comparing Pigtail Catheter and Chest Tube as the Initial Treatment for Pneumothorax. Chest. 2018; 153(5):1201-12.

187. Carden A, Dhillion T, Salcedo E, Nishijima D, Shatz D, Galante J. Systematic Review and Meta-Analysis of Pigtail Catheter Use in Traumatic Pneumothorax and Hemothorax. Jacobs Journal of Emergency Medicine. 2017; 4(1):036.

188. Williamson P, Altman D, Bagley H, Barnes K, Blazeby J, Brookes S, et al. The COMET Handook: Version 1.0. Trials. 2017; 18(Suppl 3):280.

189. Comet Initiative. Comet Initiative: Core Outcomes Measures in Effectiveness Trials. 2020 [internet]. [cited 5th August 2020]. Available from: http://www.comet-initiative.org/

190. Dubois M-J, Bergeron N, Dumont M, Dial S, Skrobik Y. Delirium in an intensive care unit: a study of risk factors. Intensive Care Medicine. 2001; 27(8):1297-304.

191. Lauretani F, Bellelli G, Pela G, Morganti S, Tagliaferri S. Treatment of Delirium in Older Persons: What We Should Not Do! International Journal of Molecular Sciences. 2020; 21(7):2397.