Online Appendix C1 BTS Guideline for Pleural Disease

Section C Pleural infection

Question C1 Evidence Review and Protocol

C1 For adults with pleural infection, what is the best predictor of clinical outcomes?

Contents

Question Evidence Review

C1 For adults with pleural infection, what is the best predictor of clinical outcomes?

Background

Pleural infection remains a common medical problem with significant mortality and morbidity despite a better understanding of the aetiology, pathophysiology and recent advances in management approaches. With a combined incidence of over 60,000 cases per annum in the USA and UK, pleural infection continues to cause a considerable burden to health systems. Understanding which patients are at greater risk of adverse outcomes may, in turn, allow clinicians to identify means by which their care can be improved to reduce mortality and morbidity. In this question we review whether there are baseline clinico-radiological markers that can predict clinical outcomes from pleural infection.

Outcomes

Mortality, need for surgery, need for re-intervention, length of hospital stay, complications, quality of life

Evidence review

The initial literature search identified 47 studies of potential relevance, of which 14 were eligible to be included in the review. Twelve of these were retrospective cohort studies[1-12], with the remaining two being prospective cohort studies[13,14]. No studies directly compared staging systems against prognostic scores or computed tomography (CT)/ultrasound (US). Instead, each study investigated one, or more clinical, microbiological or radiological predictor(s) (Table C1a) and hence this review has been approached as a prognostic review.

Mortality

All studies reported on mortality, but heterogeneity in pleural infection predictor type and differences in mortality data format limited the ability to meta-analyse the data. Data are presented by parameter type groupings as detailed in Table C1a (microbiological parameters, radiological parameters and clinical parameters).

Microbiological parameters

Three studies compared the relationship between microbiological parameters in pleural infection and mortality and a summary of the data is shown in Table C1b.[1,4,6]

Radiological parameters

Three studies also compared radiological parameters and mortality rate. One study compared US septated versus non-septated effusion[2], a second compared US complex septated versus complex non-septated effusion[3] and the third study investigated the ability of a scoring system based on CT radiological features (pleural contrast enhancement, pleural microbubbles, increased attenuation of extra-pleural fat and pleural fluid volume >400ml) for identifying complicated parapneumonic effusion (CPPE) (defined as CT score ≥4)[7]. A summary of the results is shown in Table C1c.

Clinical parameters

Six studies compared clinical parameters in pleural infection with mortality rate, with five using the RAPID (renal, age, purulence, infection source, dietary factors) risk stratification score for pleural infection[8-11,13] and one comparing three different scoring systems, CCIS (Charlson comorbidity index score), CHADS2 (congestive heart failure, hypertension, age, diabetes, previous stroke/transient ischemic attack) and CHAD2DS2-Vasc (congestive heart failure, hypertension, age, diabetes mellitus, stroke or transient ischemic attack, vascular disease, sex)[12].

Table C1a: Indicated predictors of pleural infection in adults

Study	Predictors of pleural infection
	Microbiological parameters
Brims 2019[1]	Community-acquired culture-positive pleural infection (CA-CPPI) versus hospital-acquired culture-positive pleural infection (HA-CPPI)
El Solh 2007[4]	Community-acquired empyema versus nursing home-acquired empyema
Meyer 2018[6]	Pleural infection culture positive versus culture negative
	Radiological parameters
Chen 2000[2]	US features septated versus non-septated effusion
Chen 2009[3]	US features complex septated versus complex non-septated effusion
Porcel 2017[7]	CT scoring system for identifying complicated parapneumonic effusion (CPPE) and non-CPPE
	Clinical parameters
Corcoran 2020[13]	RAPID score
Rahman 2014[8]	RAPID score
Touray 2018[9]	RAPID score
White 2015[10]	RAPID score
Wong 2016[11]	RAPID score
Davies 1999[14]	Pleural fluid (PF) purulence, PF culture positivity
Kim 2016[5]	Fever, low Hb and PaO_2, high neutrophils, microbiology
Wu 2018[12]	CCIS, CHADS2, CHAD2DS2-Vasc scores

CCIS – Charlson Comorbidity Index Score

CHADS2 – Congestive heart failure, Hypertension, Age, Diabetes, previous Stroke/transient ischemic attack

CHAD2DS2-Vasc – congestive heart failure, hypertension, age, diabetes mellitus, stroke or transient ischemic attack, vascular disease, sex category

RAPID – Renal, Age, Purulence, Infection source, Dietary factors

Table C1b: Comparison of mortality rate and microbiological parameters in adults with pleural infection

Study	Time	Predictor	**Mortality rate** (no. patients)		*p*
			Known etiology	*Negative etiology*	
Meyer 2018[6]	30 day	Pleural infection	8% (16/200)	9% (19/216)	0.76
	90 day	Pleural infection	10% (21/200)	14% (31/216)	0.21
			Community acquired	*Health-care associated*	
Brims 2019[1]	1 year	CPPI	32% (53/164)	45% (181/398)	0.006
El Solh 2007[4]	In-hospital	Empyema	8% (9/114)	18% (10/55)	0.09

CPPI – culture-positive pleural infection

Table C1c: Comparison of mortality rate and radiological parameters in adults with pleural infection

Study	**Imaging modality**	**Mortality rate** (no. patients)		***p***
		Septated	*Non-septated*	
Chen 2000[2]	US	11% (9/83)	16% (19/80)	0.313
		Complex septated	*Complex non-septated*	
Chen 2009[3]	US	21% (17/81)	7% (4/60)	0.018
		CT scoring predicted mortality/need for surgery (AUC [95% CI])*		
Porcel 2017[7]	CT	0.77 [0.62-0.92]		NA

* Composite outcome predicting need for surgery and/or mortality

AUC – area under the curve; CT – computed tomography; NA – not applicable; US – ultrasound

RAPID

The RAPID score for pleural infection was first described in 2014 and takes into account serum urea level, age, pleural fluid purulence, infection source, and serum albumin levels to risk stratify patients into low-, medium- or high-risk groups (Table C1d).[8]

Table C1d: RAPID score

Parameter	**Measure**		**Score**
Renal	Urea (mmol/L)	< 5.0	0
		5.0 – 8.0	1
		> 8.0	2
Age	< 50 years		0
	50-70 years		1
	> 70 years		2
Purulence of pleural fluid	Purulent		0
	Non-purulent		1
Infection Source	Community acquired		0
	Hospital acquired		1
Dietary factor	Albumin (g/L)	>27.0	0
		< 27.0	1
Risk category	Score 0-2		Low risk
	Score 3-4		Medium risk
	Score 5-7		High risk

Four studies (one prospective validation study[13] and three retrospective studies[8-10]) investigated the effect of RAPID scores (low (0-2), medium (3-4) and high (5-7)) on mortality at three months[8-10,13] and two reported mortality at one year[10,13]. A summary of the meta-analyses data is shown in Table C1e (corresponding meta-analyses forest plots are in Figures C1a – C1f respectively).

The final study investigating the use of RAPID scores did not include raw data to include in a meta-analysis, but instead reported a significantly higher incidence of mortality in both the medium RAPID score group and high RAPID score group when compared with the low RAPID score group ($p = 0.036$ and 0.026 respectively).[11]

Table C1e: Comparison of the risk of mortality with low, medium and high RAPID scores

Intervention	Comparator	No. datasets	**Risk of mortality** (per 1000 patients) Intervention	Comparator
			Mortality at 3 months	
Low RAPID score	Medium RAPID score	4	25 (13 to 51)	108
Medium RAPID score	High RAPID score	4	113 (80 to 161)	322
High RAPID score	Low RAPID score	4	303 (150 to 612)	24
			Mortality at 1 year	
Low RAPID score	Medium RAPID score	2	78 (48 to 126)	201
Medium RAPID score	High RAPID score	2	207 (155 to 275)	518
High RAPID score	Low RAPID score	2	469 (301 to 731)	75

CCIS, CHADS2, CHAD2DS2-Vasc scores

Wu et al compared three risk stratification scores (CCIS, CHADS2 and CHAD2DS2-Vasc) against mortality rate and a summary of the results is shown in Table C1f.[12]

Table C1f: Comparison of mortality rates across different risk stratification scoring systems (CCIS, CHADS2 and CHAD2DS2-Vasc)

Score type / Score	**Mortality rate** (no. patients) 0-1	2-3	>3	*p*
CCIS	9% (18/191)	29% (42/147)	52% (76/146)	<0.001
CHADS2	23% (371/315)	38% (51/134)	40% (14/35)	0.002
CHA2DS2-Vasc	16% (29/184)	32% (59/185)	42% (48/115)	<0.001

CCIS – Charlson Comorbidity Index Score

CHADS2 – Congestive heart failure, Hypertension, Age, Diabetes, previous Stroke/transient ischemic attack

CHAD2DS2-Vasc – congestive heart failure, hypertension, age, diabetes mellitus, stroke or transient ischemic attack, vascular disease, sex category

Although all scoring systems (CCIS, CHADS2 and CHAD2DS2-Vasc) showed an increase in mortality with increasing score levels, C-statistic comparisons showed a higher degree of mortality prediction accuracy with CCIS when compared with CHADS2 and CHAD2DS2-Vasc (z = 0.1300, p <0.001 and z = 0.1178, p <0.001 respectively, CHADS2 versus CHA2DS2-VASc z = −0.0121, p = 0.2504).[12] It should be noted, however, that CCIS has not yet been validated prospectively.

Need for surgery

Five studies reported on the need for surgery.[1,2,6,7,13]

Microbiological parameters

Two studies assessed the need for surgery based on microbiological parameters in pleural infection and a summary of the data is shown in Table C1g.[1,6]

Table C1g: Comparison of the need for surgery and microbiological parameters in adults with pleural infection

Study	**Predictor**	**Rate of need for surgery** (no. patients)		***p***
		Culture positive	*Culture negative*	
Meyer 2018[6]	Pleural infection	14% (29/200)	15% (32/216)	0.88
		Community acquired	*Hospital acquired*	
Brims 2019[1]	CPPI	18% (29/164)	17% (67/398)	0.90

CPPI - culture-positive pleural infection

Radiological parameters

Two studies also compared radiological parameters and the need for surgery. Chen et al showed a greater need for surgery in those with septated effusions, detected by US (24%, 20/83 subjects) compared to those without septations (8%, 6/80 subjects) ($p = 0.004$).[2] Porcel et al also reported an AUC of 0.77 (0.62-0.92) as a composite outcome of need for surgery/mortality for those scoring > 4 in their CT scoring system.[7]

Clinical parameters

Only one study reported on adult pleural infection clinical parameters and the need for surgery.[13] [In this study, 19.1% of participants (36/188) with a low RAPID score, 15.6% (31/199) with a medium RAPID score and 5.9% (5/85) with a high RAPID score underwent further surgery, but this may not be fully conclusive as surgeons may be less likely to operate on frail or unwell patients.

Need for repeat intervention

No studies directly reported on the need for re-intervention (defined as any procedure undertaken to remove infected pleural fluid and/or clear the pleural space of infection and debris), but two studies reported on the rate of treatment failure, which may infer a need for re-intervention[3,4].

Microbiological parameters

One study investigating microbiological predictors saw a 37% (42/114 subjects) failure rate in community acquired pleural infection compared with 61% (34/55) in healthcare associated pleural infection ($p = 0.01$).[4]

Radiological parameters

Another study exploring radiological predictors reported a 49% (40/81 subjects) treatment failure rate with complex septated effusions compared with a 20% (12/60) failure rate with complex non-septated effusions ($p = 0.001$).[3]

A further study specifically investigating predictors of outcome and survival in pleural infection grouped their participants by treatment success and treatment failure and showed that 77% of those with treatment failure (10/13) had pleural fluid purulence, whereas 40% of those with treatment success (29/72) had pleural fluid purulence ($p = 0.02$).[14]

Length of hospital stay

Length of hospital stay was reported in six studies investigating predictors of pleural infection of adults.

Microbiological parameters

Three studies compared the effect of different microbiological parameters on length of hospital stay and the data are summarised in Table C1h.[1,4,6]

Table C1h: The effect of pleural infection microbiological parameters on length of hospital stay

Study	Predictor	**Length of hospital stay** (days) (median [IQR or range*])		*p*
		Culture positive	*Culture negative*	
Meyer 2018[6]	Pleural infection	16	18	0.22
		Community acquired	*Health-care associated*	
Brims 2019[1]	CPPI	15 [8-28]	19 [11-37]	0.001
El-Solh 2007[4]	Empyema	13 [4-181]	21 [7-177]	0.006

CPPI - culture-positive pleural infection; IQR – interquartile range

Radiological parameters

Similarly, two studies compared the effect of radiological parameters on length of hospital stay and a summary of the data is shown in Table C1i.[2,3]

Table C1i: Comparison of mortality rate and radiological parameters in adults with pleural infection

Study	Imaging modality	**Length of hospital stay** (days) (mean ± SD)		*p*
		Septated	*Non-septated*	
Chen 2000[2]	US	35.4 ± 2.7	27.0 ± 1.6	0.009
		Complex septated	*Complex non-septated*	
Chen 2009[3]	US	33.6 ± 34.5	33.2 ± 36.1	NS

NS – not significant; US – ultrasound

Clinical parameters

Table C1j: Summary of microbiological and clinical parameters linked to long length of hospital stay

Microbiological /clinical parameter	**Adjusted* Odds Ratio [OR] for increased length of stay**	*p*
Microbiological parameter		
Positive Identification of microbes	4.14 [1.14-15.05]	0.03
Clinical parameters		
Hb <12 g/dL	4.90 [1.71-14.04]	0.003
PaO_2 < 70 mmHg	4.89 [1.55-15.47]	0.007
Blood neutrophil fraction	3.83 [1.32-11.13]	0.01
Fever	3.42 [12.6-9.29]	0.02
Ineffective drainage	3.28 [1.13-9.54]	0.03

* Adjusted for age and CURB-65 score

CURB-65 – (confusion, urea, respiratory rate, blood pressure, aged ≥65 years) score for predicting mortality in community-acquired pneumonia; Hb – haemoglobin; PaO_2 – partial pressure of oxygen

Only one study compared clinical parameters against length of hospital stay showing an increase in length of hospital stay with corresponding increase in RAPID score (11 (6 to 21) days, 13 (7 to 25) days and 18 (10 to

27) days for low RAPID scores [0-2], medium RAPID scores [3-4] and high rapid scores [5-7] respectively, $p = 0.003$).[13]

A final study compared microbiological and clinical parameters against long and short hospital stays, defined as >18 days and ≤18 days respectively, and identified six microbiological and clinical parameters that were significantly linked to a long length of hospital stay (>18 days) (Table C1j).[5]

Complications and quality of life

No studies compared pleural infection predictors with complications or quality of life.

Evidence statements

Microbiology parameters

Based on limited evidence:

Pleural infection causative organism does not appear to have an effect on predicting mortality rate, hospital length of stay or the need for thoracic surgery in adults with pleural infection (**Ungraded**)

Healthcare-acquired pleural infection may increase mortality rate and increase hospital length of stay when compared with community-acquired pleural infection in adults (**Ungraded**)

Radiological parameters

The presence of septated features on ultrasound (US) features in adults with pleural infection may be associated with an increased length of hospital stay and an increased need for thoracic surgery when compared with non-septated US features (**Ungraded**)

The presence of complex septated ultrasound (US) features may be associated with an increased mortality rate, an increased treatment failure rate and an increased length of hospital stay when compared with complex non-septated US features (**Ungraded**)

A parapneumonic effusion CT scoring system may show acceptable discrimination for predicting mortality and/or the need for surgery (**Ungraded**)

Clinical parameters

Higher RAPID scores appear to indicate an increased risk of mortality (**Low***) and may indicate an increased length of hospital stay (**Ungraded**)

The Charlson comorbidity index score (CCIS) is associated with may also indicate an increased risk of mortality with increased CCIS score (**Ungraded**)

** Based on an average of all presented GRADE scores*

Recommendation

- RAPID scoring should be considered for risk stratifying adults with pleural infection and can be used to inform discussions with patients regarding potential outcome from infection (**Conditional**)

Research Recommendations

- Further research is needed into assessing the potential role of radiology (ultrasound and computed tomography) in risk stratification of patients presenting with pleural infection
- Further research is needed to assess if directed care according to RAPID scores effects clinical outcome

Meta-analyses

Figure C1a: Mortality at 3 months, low versus medium RAPID scores

Study or Subgroup	Low score Events	Low score Total	Medium score Events	Medium score Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Corcoran 2020	5	222	21	228	50.7%	0.24 [0.09, 0.64]
Rahman 2014	3	97	6	65	17.6%	0.34 [0.09, 1.29]
Touray 2018	1	19	4	48	5.6%	0.63 [0.08, 5.29]
White 2015	0	43	13	66	26.2%	0.06 [0.00, 0.92]
Total (95% CI)		**381**		**407**	**100.0%**	**0.23 [0.12, 0.47]**
Total events	9		44			
Heterogeneity: Chi² = 2.12, df = 3 (P = 0.55); I² = 0%						
Test for overall effect: Z = 4.06 (P < 0.0001)						

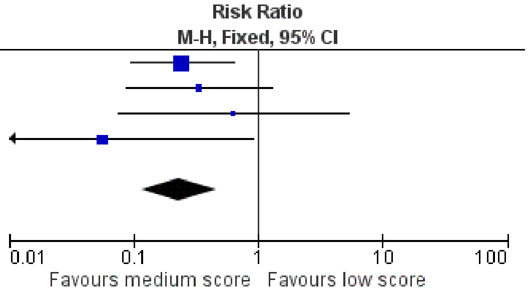


Figure C1b: Mortality at 3 months, medium versus high RAPID scores

Study or Subgroup	Medium score Events	Medium score Total	High score Events	High score Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Corcoran 2020	21	228	27	92	45.8%	0.31 [0.19, 0.53]
Rahman 2014	6	65	9	29	14.8%	0.30 [0.12, 0.76]
Touray 2018	4	48	7	31	10.1%	0.37 [0.12, 1.16]
White 2015	13	66	21	47	29.2%	0.44 [0.25, 0.79]
Total (95% CI)		**407**		**199**	**100.0%**	**0.35 [0.25, 0.50]**
Total events	44		64			
Heterogeneity: Chi² = 0.89, df = 3 (P = 0.83); I² = 0%						
Test for overall effect: Z = 5.98 (P < 0.00001)						

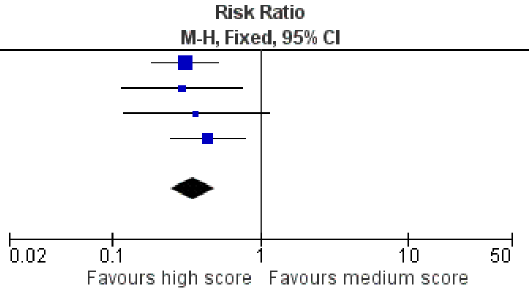


Figure C1c: Mortality at 3 months, high versus low RAPID scores

Study or Subgroup	Low score Events	Low score Total	High score Events	High score Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Corcoran 2020	5	222	27	92	49.0%	0.08 [0.03, 0.19]
Rahman 2014	3	97	9	29	17.8%	0.10 [0.03, 0.34]
Touray 2018	1	19	7	31	6.8%	0.23 [0.03, 1.75]
White 2015	0	43	21	47	26.4%	0.03 [0.00, 0.41]
Total (95% CI)		**381**		**199**	**100.0%**	**0.08 [0.04, 0.16]**
Total events	9		64			
Heterogeneity: Chi² = 1.92, df = 3 (P = 0.59); I² = 0%						
Test for overall effect: Z = 7.11 (P < 0.00001)						

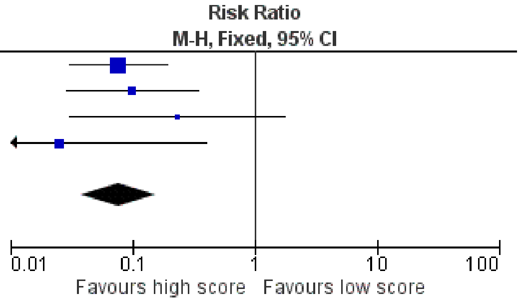


Figure C1d: Mortality at 1 year, low versus medium RAPID scores

Study or Subgroup	Low score Events	Low score Total	Medium score Events	Medium score Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Corcoran 2020	14	222	41	228	74.0%	0.35 [0.20, 0.63]
White 2015	6	43	18	66	26.0%	0.51 [0.22, 1.19]
Total (95% CI)		**265**		**294**	**100.0%**	**0.39 [0.24, 0.63]**
Total events	20		59			
Heterogeneity: Chi² = 0.53, df = 1 (P = 0.47); I² = 0%						
Test for overall effect: Z = 3.86 (P = 0.0001)						

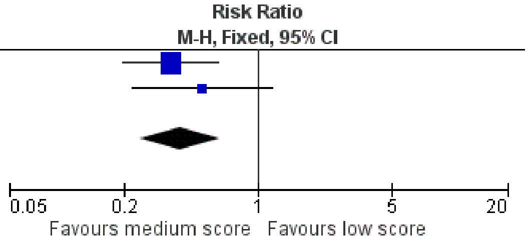


Figure C1e: Mortality at 3 months, medium versus high RAPID scores

Study or Subgroup	Medium score Events	Medium score Total	High score Events	High score Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Corcoran 2020	41	228	46	92	68.3%	0.36 [0.25, 0.51]
White 2015	18	66	26	47	31.7%	0.49 [0.31, 0.79]
Total (95% CI)		**294**		**139**	**100.0%**	**0.40 [0.30, 0.53]**
Total events	59		72			

Heterogeneity: Chi² = 1.12, df = 1 (P = 0.29); I² = 11%
Test for overall effect: Z = 6.45 (P < 0.00001)

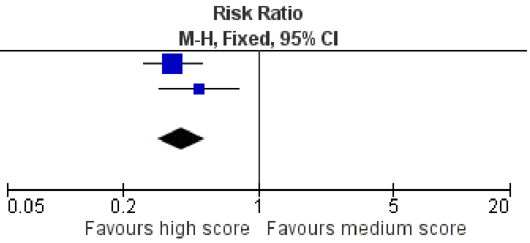
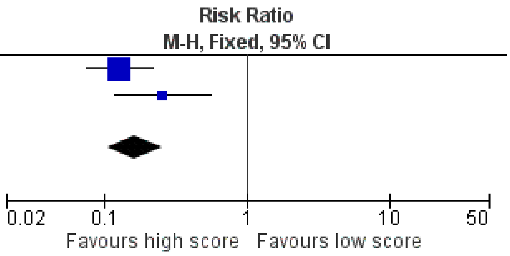


Figure C1f: Mortality at 1 year, low versus high RAPID scores

Study or Subgroup	Low score Events	Low score Total	High score Events	High score Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Corcoran 2020	14	222	46	92	72.4%	0.13 [0.07, 0.22]
White 2015	6	43	26	47	27.6%	0.25 [0.11, 0.55]
Total (95% CI)		**265**		**139**	**100.0%**	**0.16 [0.10, 0.25]**
Total events	20		72			

Heterogeneity: Chi² = 2.02, df = 1 (P = 0.16); I² = 51%
Test for overall effect: Z = 8.08 (P < 0.00001)



Risk of bias summary

	Selection bias	Detection bias	Attrition bias	Publication bias
Brims 2019	+	?	?	+
Chen 2000	+	?	?	+
Chen 2009	?	?	+	+
Corcoran 2020	+	+	+	+
Davies 1999	−	?	+	+
El Solh 2007	+	?	?	+
Kim 2016	+	?	?	+
Meyer 2018	+	?	?	+
Porcel 2017	+	+	+	+
Rahman 2014	+	?	+	+
Suarez 2012	−	−	?	+
Touray 2018	+	?	+	+
White 2015	+	?	?	+
Wong 2016	+	?	?	+
Wu 2018	+	?	?	+

GRADE analyses

For adults with pleural infection, what is the best predictor of clinical outcomes?

Population: Adults (18+) with pleural infection

Predictor: Low RAPID score [0 – 2]

Comparator: Medium RAPID score [3 – 4]

Outcome	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects		Quality of the Evidence (GRADE)
			Medium RAPID	Low RAPID	
Mortality at 3 months	788 (4 studies)	RR 0.23 (0.12 to 0.47)	**108 per 1000**	**25 per 1000** (13 to 51)	⊕◯◯◯ **VERY LOW** [a,b,c]
Mortality at 1 year	559 (2 studies)	RR 0.39 (0.24 to 0.63)	**201 per 1000**	**78 per 1000** (48 to 126)	⊕⊕⊕◯ **MODERATE** [a]

CI: Confidence interval

Explanations

a. Some risk of bias across the studies
b. Some inconsistency across the studies
c. GRADE score downgraded by one as primary study type retrospective

For adults with pleural infection, what is the best predictor of clinical outcomes?

Population: Adults (18+) with pleural infection

Predictor: Medium RAPID score [3 – 4]

Comparator: High RAPID score [5 – 7]

Outcome	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects		Quality of the Evidence (GRADE)
			High RAPID	Medium RAPID	
Mortality at 3 months	606 (4 studies)	RR 0.35 (0.25 to 0.50)	**322 per 1000**	**113 per 1000** (80 to 161)	⊕⊕◯◯ **LOW** [a,b]
Mortality at 1 year	433 (2 studies)	RR 0.40 (0.30 to 0.53)	**518 per 1000**	**207 per 1000** (155 to 275)	⊕⊕⊕◯ **MODERATE** [a]

CI: Confidence interval

Explanations

a. Some risk of bias across the studies
b. GRADE score downgraded by one as primary study type retrospective

For adults with pleural infection, what is the best predictor of clinical outcomes?

Population: Adults (18+) with pleural infection

Predictor: Low RAPID score [0 – 2]

Comparator: High RAPID score [5 – 7]

Outcome	Number of participants (studies)	Relative effect (95% CI)	Anticipated absolute effects		Quality of the Evidence (GRADE)
			High RAPID	Low RAPID	
Mortality at 3 months	580 (4 studies)	RR 0.08 (0.04 to 0.16)	**322 per 1000**	**26 per 1000** (13 to 51)	⨁◯◯◯ **VERY LOW** [a,b,c]
Mortality at 1 year	404 (2 studies)	RR 0.16 (0.10 to 0.25)	**518 per 1000**	**83 per 1000** (52 to 129)	⨁⨁⨁◯ **MODERATE** [a]

CI: Confidence interval

Explanations

a. Some risk of bias across the studies

b. Some inconsistency across the studies

c. GRADE score downgraded by one as primary study type retrospective

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Question Protocol

Field	Content
Review Question	For adults with pleural infection, what is the best predictor of clinical outcomes?
Type of review question	Intervention review
Objective of the review	Pleural infection is associated with poor clinical outcomes including long hospital stay, mortality and the need for surgery. Are there baseline clinical, radiological or biochemical parameters which predict which patients might have a bad clinical outcome?
Eligibility criteria – population / disease / condition / issue / domain	Adults (18+) with pleural infection
Eligibility criteria – intervention(s)	Staging system
Eligibility criteria – comparators(s)	Prognostic scores CT and ultrasound
Outcomes and prioritisation	Mortality Need for surgery Need for re-intervention Length of hospital stay Complications Quality of life
Eligibility criteria – study design	RCTs Prospective comparative studies Case series of >100 patients
Other inclusion /exclusion criteria	Non-English language excluded unless full English translation Conference abstracts, Cochrane reviews, systematic reviews, reviews Cochrane reviews and systematic reviews can be referenced in the text, but **DO NOT** use in a meta-analysis
Proposed sensitivity / subgroup analysis, or meta-regression	None

Selection process – duplicate screening / selection / analysis	Agreement should be reached between Guideline members who are working on the question. If no agreement can be reached, a decision should be made by the Guideline co-chairs. If there is still no decision, the matter should be brought to the Guideline group and a decision will be made by consensus
Data management (software)	RevMan5 — Pairwise meta-analyses Evidence review/considered judgement. Storing Guideline text, tables, figures, etc. Gradeprofiler — Quality of evidence assessment Gradepro — Recommendations
Information sources – databases and dates	MEDLINE, Embase, PubMED, Central Register of Controlled Trials and Cochrane Database of Systematic Reviews 1966 - present
Methods for assessing bias at outcome / study level	RevMan5 intervention review template and NICE risk of bias checklist (follow instructions in '*BTS Guideline Process Handbook – Intervention Review'*)
Methods for quantitative analysis – combining studies and exploring (in)consistency	If 3 or more relevant studies: RevMan5 for meta-analysis, heterogeneity testing and forest plots (follow instructions in '*BTS Guideline Process Handbook – Intervention Review'*)
Meta-bias assessment – publication bias, selective reporting bias	GRADEprofiler — Intervention review quality of evidence assessment for each outcome (follow instructions in '*BTS Guideline Process Handbook – Intervention Review'*)
Rationale / context – what is known	Knowledge of which patients might have a poor clinical outcome may allow patients to be triaged to more aggressive treatments and improve outcomes. What is the evidence for baseline factors predicting clinical outcomes?