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Hospital Acquired Pneumonia and Frailty: The New Old Age Problem to Solve

Novel scoping review and case study investigation of hospital acquired pneumonia risk factors and frailty

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Thesis

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Declaration

'Yr wyf drwy hyn yn datgan mai canlyniad fy ymchwil fy hun yw'r thesis hwn, ac eithrio lle nodir yn wahanol. Caiff ffynonellau eraill eu cydnabod gan droednodiadau yn rhoi cyfeiriadau eglur. Nid yw sylwedd y gwaith hwn wedi cael ei dderbyn o'r blaen ar gyfer unrhyw radd, ac nid yw'n cael ei gyflwyno ar yr un pryd mewn ymgeisiaeth am unrhyw radd oni bai ei fod, fel y cytunwyd gan y Brifysgol, am gymwysterau deuol cymeradwy.'

Rwy'n cadarnhau fy mod yn cyflwyno'r gwaith gyda chytundeb fy Ngrichwyliwr (Goruchwylwyr)'

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Bangor University

Master of Science by Research (MScRes)

Hospital Acquired Pneumonia and Frailty:

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Dr. P. M. Kempster MBChB

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Thesis abstract

Infections acquired in hospital, known as 'nosocomial infections' are an important issue across the globe. They have immense health and economic cost and need to be addressed urgently. One form of these diseases is hospital acquired pneumonia (HAP) and it carries the highest mortality of all nosocomial infections. HAP is poorly studied outside of intensive care units and therefore was the focus of this thesis. Frailty, a similarly important problem in global populations is an emerging area of interest and also of personal interest to the researcher. This latter problem was studied later on in this work as it emerged as a possible issue in the context of HAP.

This thesis consists of four chapters; the first introduces the topics of interest, contextualises them and introduces the two novel pieces of work. The second describes a scoping review of the literature exploring risk factors for acquisition and mortality from HAP. This scoping review informs the third chapter where a novel pilot study into frailty in the context of HAP is described. The final chapter of this thesis then concludes with a summary of the work with further contextualisation, synthesis of concepts and recommendations for policy, research and practice.

The outcome of the scoping review was a synthesis of novel models describing the evidence. A novel model explaining how patients are put at risk of acquiring HAP was produced, as was a model for how the literature was found to be fractured. It also concluded that further research into HAP mortality risk was urgently needed to allow a similar model for risk to be produced. The novel pilot study performed in Chapter Three studied the issue of frailty and its relationship to HAP after frailty emerged as an important issue. It therefore began the work to produce a model for HAP mortality. The thesis concludes by stating that further research is urgently needed and recommendations for focus and methodology are made. Further research into the issue of frailty in the context of HAP is urgently needed, more specifically the relationship between frailty and mortality. This will continue the work in Chapter Three and aid the production of new models. These models may then be able to inform patient care.

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Chapter One

Hospital Acquired Pneumonia, Frailty and the Thesis: The Context

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1.0 Introduction

The purpose of this thesis was to explore the subject of hospital acquired pneumonia (HAP) and discover novel findings. The focus of study was on the risk factors surrounding HAP acquisition and mortality risk. Of these risk factors, the involvement of the complex issue of frailty was of particular interest.

Chapter One of this thesis introduces the topics of interest and explains how they were studied in Chapters Two and Three via means of a scoping review and a pilot study. The final chapter of the thesis draws together the findings, synthesis and conclusions and provides recommendations for policy, research and practice.

The scoping review in Chapter Two explored the literature surrounding HAP and aimed to identify, summarise and synthesise the risk factors for acquisition and mortality of HAP. This then informed the work undertaken and reported in Chapter Three by identifying novel areas where further study was needed.

The exploratory pilot study in Chapter Three explored the relationship between frailty score and key elements of HAP: the presentation, progression and outcomes. The aim was to add to the literature regarding the issue of frailty in the context of HAP and the relationships between the two. This would then hopefully improve understanding of the importance of frailty and help to improve the understanding of HAP.

It was hoped that seeking to improve understanding of HAP would add to the collective scientific understanding of nosocomial infections. This is the key to any attempts at reducing the burden of these diseases.

1.1 Background: nosocomial infections

Nosocomial infections are infections that are acquired in hospital. By definition they cannot be developing or present on admission to hospital or healthcare settings (WHO, 2002). Occasionally they can become apparent after discharge having been acquired during the admission. There are several different types of nosocomial infections including (but not limited to): pneumonias, skin and soft tissue infections and gastrointestinal infections. Any body system can in fact be affected by a nosocomial infection (Garner et al., 1988).

According to the World Health Organisation (WHO) (2011), nosocomial infections affect patients in all healthcare settings across the globe and are the most frequent adverse event seen in such places. It is estimated by the European Centre for Disease Prevention and Control (ECDC) (2008), that over 4 million patients are affected by these diseases annually in Europe. Nosocomial infections result in prolonged admissions, disability and additional deaths and all of these outcomes result in increased financial cost to healthcare systems (ECDC, 2008). Another potential deadly outcome of nosocomial infections results from the need to treat such diseases with antimicrobials. The more times antimicrobials are used to treat infections the greater probability that antimicrobial resistance develops. Increasing global anti-microbial resistance is an emerging issue and is thus made worse as antimicrobials are administered for nosocomial infections that could otherwise have been avoided (WHO, 2011).

An additional consequence of nosocomial infections is an increased length of stay. This has both a health and financial cost (WHO, 2011). Ultimately, any financial cost results in a health cost as money cannot be spent on other treatments or research. A review of the literature by the WHO (2011) discovered that the increased length of stay due to nosocomial infections ranges from 5 to 29.5 days. The ECDC estimated that approximately 7 billion euros annually are spent directly tackling nosocomial infections in Europe (ECDC, 2008). In the USA alone in 2004, this cost was 6.5 billion dollars (Klevens et al., 2007).

Within the National Health Service (NHS) in the United Kingdom (UK), the effects of nosocomial infections are enormous. It is estimated that in 2016/2017 there were 834,000 nosocomial infections within NHS hospitals in England, of which 28,500 proved fatal. The cost of this to the NHS was estimated to be an extra 2.7 billion pounds and 7.1 million occupied hospital bed days (Guest et al., 2020).

The burden of nosocomial infections across the globe and here in the UK is clearly enormous. The WHO states that studying this burden is vital to identify mitigation strategies (WHO, 2011). If the

collective understanding of how to prevent and treat these diseases is improved compared to current levels then it may be possible to reduce the frequency of the above sequelae. In the publically funded NHS it is vital that money is saved where it can be used to fund other treatments. It has been known for some time that methods to reduce nosocomial infections can be very effective, which would be of clear benefit to reduce the associated morbidity, mortality and monetary costs described above (Hayley et al., 1985). A literature review by the WHO has found many examples of such methods (WHO, 2011). Common sense would dictate that the first priority should be on the nosocomial infections that have the greatest impact.

1.2 Background: hospital acquired pneumonia

The nosocomial infection with the highest death rate is nosocomial pneumonia. This type of nosocomial infection is also the second most common form of such illnesses (Nair & Neiderman, 2013). Nosocomial pneumonia is defined as a new lower respiratory tract infection that develops 48 hours or later into a patient's admission to hospital. There are three distinct subtypes of nosocomial pneumonia: hospital acquired pneumonia, ventilator associated pneumonia and healthcare associated pneumonia (Nair & Neiderman, 2013).

The focus of study in this thesis was hospital acquired pneumonia (HAP). This disease is one variety of nosocomial pneumonia and is thus one variety of nosocomial infection. The study of this disease may therefore add to the collective global effort of reducing the burden of nosocomial infections. HAP was chosen as the nosocomial infection of interest for this thesis after a preliminary literature search revealed that it was poorly studied outside of intensive care units (Sopena et al., 2014; Burton et al., 2016).

1.4 Background: frailty

An important emergent issue in the context of HAP is identified in Chapter Two that demands further attention. This is the issue of frailty and it is explored further via the exploratory pilot study described within Chapter Three.

Frailty manifests as a vulnerability to change in health due to minor insults from illness or injury and has been deemed to be the most problematic consequence of an ageing population (Clegg et al., 2013). Frailty is associated with many chronic diseases including respiratory and cardiovascular disease and it is more common if two or more diseases are present (Fried et al., 2001). It is a separate and distinct entity to both comorbidity and disability and increases the risk of many adverse outcomes, including falls, delirium, hospitalisation and death (Fried et al., 2001; Clegg et al., 2013).

To the researcher's knowledge, frailty as a risk factor for mortality from HAP had not been studied previously. The scoping review in Chapter Two identified that more work was needed to study the relationship between performance status or general deterioration and HAP acquisition or mortality. Performance status and general deterioration are separate to frailty but form part of the syndrome and contribute to a patient's frailty 'level' (Rockwood et al., 2005).

The frailty 'level' of a patient can be represented on a scale whereby increasing numbers represent increasing 'levels' of frailty. There are several interpretations and methods by which frailty is stratified in this way. The system familiar to the researcher and that which is used in the hospital where the research was undertaken was that devised by Rockwood et al (2005) (appendix 1). This linear scale corresponds to qualitative descriptions of what a patient is or isn't able to do and ranges from 1- where a patient is completely independent to 9- where a patient is terminally ill.

If frailty can increase the risk of hospitalisation, then clearly via this outcome it will increase the risk of nosocomial infections (i.e. a more frail individual is more likely to have nosocomial infections as they are more likely to be admitted to hospital). However, this thesis aimed to assess the importance of a patient's frailty 'level'- as represented by their frailty score, for hospitalised patients who acquired HAP regarding their progression and mortality. As frailty is associated with an increased risk of death and other negative outcomes (Fried et al., 2001; Clegg et al., 2013), it was hypothesised that a higher frailty score would increase the risk of dying from HAP or affect how it presented. This is explored in Chapter Three through a piece of novel empirical research.

The importance of this concept cannot be understated. It is well known that the UK has an ageing population, as do many other countries around the world (Cosco et al., 2017). As the NHS has to adapt to meet these changes it is vital that clinicians, researchers and policy makers are aware of the particular issues that an ageing population brings with it. As frailty is known to be a consequence of ageing (Clegg et al., 2013), it follows that an ageing population will also be a more frail population (Hoogendijk et al., 2019). If increasing frailty is shown to impact on the presentation and progression

of HAP, or risk of mortality from HAP, then healthcare systems can adapt further to mitigate against this important nosocomial infection. A call for the adaptation of healthcare systems and care based on an understanding of frailty has recently been made (Cesari et al., 2017).

1.5 Thesis structure

Chapter One

Chapter One describes the broad scope of interest for this thesis. It also begins to explain why the issues of HAP and frailty are important and how they are studied in this thesis. Nosocomial infections are important diseases (WHO, 2011) and hospital acquired pneumonia is one form of nosocomial infection that is poorly researched and demands attention (Nair & Neiderman, 2013; Sopena et al., 2014; Burton et al., 2016). Frailty is an important problem in the ageing population and therefore similarly demands attention (Clegg et al., 2013).

Chapter Two

Chapter Two of this thesis describes a scoping review of the available literature on HAP. More specifically it describes a study examining the evidence surrounding risk factors for acquisition and mortality from HAP. To the researcher's knowledge a scoping review of this subject had not been performed prior to this thesis. Clearly, if risk factors could be identified that could be mitigated then the above issues surrounding HAP and nosocomial infections could be reduced.

The review aimed to pull these risk factors together and summarise current understanding. Through thematic analysis and synthesis of these findings the literature could be summarised and models describing the evidence base for risk factors for HAP acquisition could be synthesised. No model could be produced for risk factors for HAP mortality due to a paucity of evidence. No papers were identified studying the relationship between performance status or general deterioration and mortality from HAP. This analysis was therefore able to inform further empirical research in the form of pilot studies by identifying these understudied areas. Such a pilot study was then undertaken by the researcher to allow initial exploration of an area of interest. It is described in Chapter Three.

Chapter Three

Chapter Three of this thesis stems from the outcomes of the scoping review in Chapter Two and aims to develop what was discovered during the scoping review via empirical research. It is comprised of an exploratory pilot study exploring important issues found to be hitherto unexplored in the literature. This study was performed in an effort to add to the knowledge gained through Chapter Two and add clarity to emergent themes. The most important novel issue first explored in Chapter Three is frailty- a clinical condition that results from a decline in physiological reserve with age (Clegg et al., 2013).

The issue of frailty is first proposed in Chapter Three as an understudied and potentially important risk factor. This is based on the findings of the scoping review in Chapter Two regarding performance status or general deterioration and mortality from HAP. The lack of study of these two areas and the resulting inability to produce a model for HAP mortality risk in Chapter Two demonstrated an area demanding further novel research. The relationship between these two risk factors and the concept of frailty is discussed in more detail in Chapter Three.

Chapter Four

Chapter Four summarises the findings of Chapter Two and Three. It brings together the important concepts and frames the issues of HAP and frailty both in the context of each other and in the context of the wider literature and global situation. It then details recommendations for policy, research and practice based on the findings of this thesis.

Chapter Two

Positioning Hospital Acquired Pneumonia: a Scoping Review

2.0 Introduction

The importance of nosocomial infections, nosocomial pneumonia and HAP were introduced in Chapter One. HAP was chosen by the researcher to be studied due to the paucity of evidence surrounding it as well as personal clinical interest of the researcher as a doctor working in respiratory medicine.

The purpose of Chapter Two of the thesis is to improve understanding of both risk factors for acquisition of HAP and risk factors for mortality from HAP. To begin this process a scoping review of the available literature was performed in order to position the issue in the context of the available literature. To the researcher's knowledge, a scoping review of this subject had not been performed prior to this thesis. The insight gained from this exploratory review then informs empirical research into the field which is the focus of Chapter Three. Together both pieces of research add to the current understanding of risk factors for HAP acquisition and mortality.

2.1 Background

Hospital acquired pneumonia (HAP) has not been well studied outside of intensive care units. The incidence is estimated to be less than 1% of overall hospital admissions but this figure rises to 8-10% of patients admitted to elderly care units (Burton et al., 2016). The researcher therefore proposed that this field deserved further research and attention. Furthermore, HAP is associated with increased risk of morbidity and mortality in affected patients, with increased length of stay in hospital and likelihood of discharge to a nursing home (Sopena et al., 2014). The risk factors for both

acquisition of HAP and mortality from HAP were therefore clearly of importance to understand. When referred to in this thesis, 'risk factors for acquisition' are any patient or healthcare related factor that increases the risk of a patient acquiring a HAP as part of their hospital admission. 'Risk factors for mortality' are any factors that increase the risk of death from HAP. It was the purpose of this scoping review to study these risk factors through analysis of the available evidence base.

This key aim of examining HAP within the framework of a scoping review was to allow a better understanding of this complex phenomenon. This could inform further research and thus enable clinicians and other healthcare professionals to adapt care processes and reduce the risk of patients developing HAP or dying as a result. Furthermore, an enhanced understanding of which risk factors were most important would facilitate the prioritisation of mitigating factors in a healthcare system that is well known to be increasingly under immense pressure. Improving the care process and reducing rates of acquisition and mortality may reduce the burden that this nosocomial infection has on societies across the globe.

2.2 Methods: scoping review principles

As part of an exploratory review of the evidence surrounding HAP a scoping review of the literature was utilised as a flexible approach to identify the nature and context of the evidence base. A scoping review is different to a systematic review in that the aim is to produce an overview of a wide range of available evidence (Ehrich et al., 2002). As an increasingly popular means of literature review, scoping reviews do not begin with a narrow and specific fixed question like in a systematic review (Davis et al., 2009). Rather, they aim to answer a much broader question which is flexible and adapted ad hoc. In this way, it allows a researcher to identify the available evidence and identify any gaps in the collective knowledge much more easily (Arksey & O'Malley, 2005). Furthermore, the aim of a scoping review is not to synthesise the data as in a systematic review. Alternatively, the aim is to provide an over-arching narrative, analysis and interpretation of the evidence base found in the literature (Levac et al., 2010).

Although the aim of a scoping review is not to assess the quality of the available evidence it can provide insights into the nature, focus and rigour of the evidence through appraisal techniques (Daudt et al., 2013). This allows the inclusion of a broader range of data which may arise from many different study designs to give a better overview. Rather than focussing on the quality of a narrow range of evidence as in a systematic review a scoping review aims to provide researchers with a

much broader overview. This therefore provides the reader with more knowledge on what has been researched, the extent it has been researched, the context it has been researched within as well as what has been discovered (Arksey & O'Malley, 2005; Levac et al., 2010).

It is the values of a scoping review mentioned above that led to this method being chosen as the optimum method by which to review the literature. The study aimed to answer a broad question, gain understanding of what the literature showed and learn how previous research had been conducted. The aim was to use this scoping review to inform future empirical work and therefore a scoping review was best placed to provide this information. Arksey and O'Malley (2005) first proposed a framework by which scoping reviews could be conducted. This methodology was later refined by Levac et al (2010) and then again by the Joanna Briggs Institute (2015). The methodological framework is comprised of a five-stage approach:

1) **Identifying the research question**
2) **Identifying relevant studies**
3) **Study selection**
4) **Charting the data**
5) **Collation, summarizing and reporting the results**

There is then an additional, optional stage six titled 'consultation' whereby results are disseminated to stakeholders (Arksey & O'Malley 2005; Levac et al., 2010).

It is this five stage methodological framework that is followed throughout this scoping review. The following description of the review is divided into the sections of the framework as it is discussed.

2.3 Methods: scoping review stages

Scoping review stage 1- Identifying the research question

As detailed earlier in this report, the research questions of interest in this study were based upon a desire to add to the current knowledge surrounding HAP. More specifically to add to the knowledge regarding risk factors for acquisition of HAP and risk factors for mortality from HAP.

The questions this scoping review aimed to answer were as follows:

1) What is currently known from the existing literature regarding the risk factors for acquisition of HAP?
2) What is currently known from the existing literature regarding the risk factors for mortality from HAP?

Scoping review stage 2- Identifying relevant studies

An initial cursory search of the literature was performed to guide the search strategy. This initial search confirmed the lack of research into HAP as previously suggested (Burton et al., 2016). Searches of the available literature using the Ovid Medline, Web of Science and Pubmed databases were performed using the following search terms:

(Hospital acquired pneumonia OR healthcare associated pneumonia OR nosocomial pneumonia) AND (risk* OR risk factor* OR odds* OR odds ratio OR prognos*). The search strategy utilised 'HCAP' (healthcare associated pneumonia) despite the scope of the work being solely interested in HAP due to the differences in how the subtypes are named in different countries. Papers were excluded if on reading it transpired that they were not studying HAP. The results of the above searches were limited to adult human populations and studies published in English. Any year of publication was included.

Scoping review stage 3- Study selection

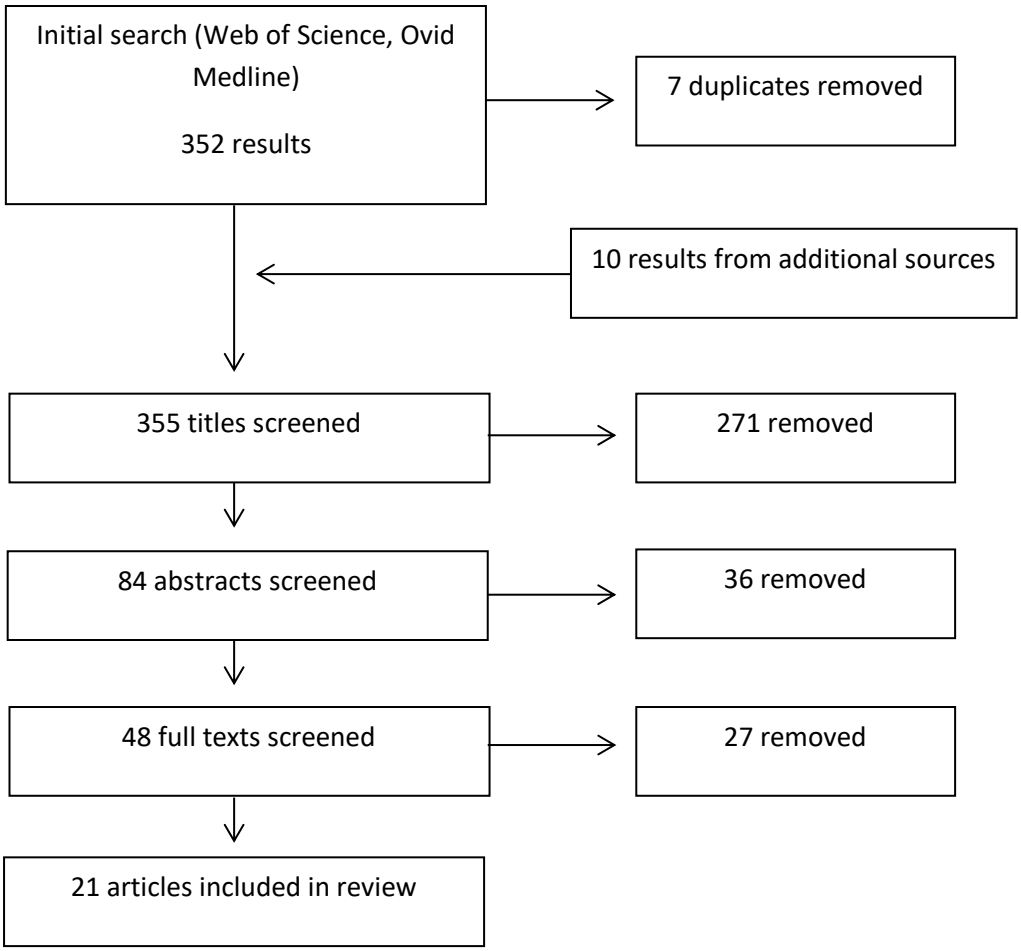
The inclusion criteria used to develop the search strategy in 'population and problems, exposure and outcome or themes' (PEO) format can be seen in Table 1.

PEO format	**Question 1**
Population and Problems	Patients who have been in hospital >48 hours
Exposure	Risk factors for acquiring HAP
Outcome or Themes	HAP diagnosis
PEO format	**Question 2**
Population and Problems	Patients who have developed HAP
Exposure	Risk factors for death from HAP
Outcome or Themes	Death from HAP

Table 1. Inclusion criteria in PEO format.

The Ovid Medline search returned 184 results, Web of Science returned 168 and additional sources (PubMed, Cochrane Collaboration, Google Scholar searches) returned 10. Figure 1 is a PRISMA diagram demonstrating the search results and filtering. In total 21 full text papers were included in the final scoping review. Reasons for exclusion from the review at the screening stages were as follow: paper studied ventilator associated pneumonia, healthcare associated pneumonia or community acquired pneumonia, currently mechanically ventilated patients or intubated patients, procedures known to cause HAP only, critical care patients only, specific pathogens or patients with specific diseases only and biochemistry only.

The focus of this scoping review, whilst broad, was only for HAP. Further research is needed into the other types of nosocomial infection but this is outside the scope of this thesis. Mechanically ventilated and intubated patients who develop a pneumonia are considered to have a VAP and therefore fall outside the scope of this thesis. Any study into a procedure which is known to cause HAP is focussed intensively into this cause and not an appropriate way to study risk factors for HAP. Papers which studied specific pathogens or diseases were deemed too specific and of little value to this study. Their results could not be included in the context of risk factors for the general population. Papers which studied biochemistry only were not of relevance.



Total	**Web of Science**	**Ovid Medline**	**Additional Sources (PubMed, Cochrane Collaboration, Google Scholar)**
352	168	184	12
Reasons for exclusion at any stage: Paper studied ventilator associated pneumonia, healthcare associated pneumonia or community acquired pneumonia, currently mechanically ventilated patients or intubated patients, procedures known to cause HAP only, critical care patients only, specific pathogens or patients with specific diseases only and biochemistry only			

Figure 1. PRISMA diagram of the literature search.

Scoping review stage 4- Charting the data

The 21 full text papers included in the review are summarised in Table 2. As per the methodology of a scoping review (Levac et al., 2010) the data was charted and collated. Table 2 details the included papers. This charting allowed data analysis to begin. Microsoft Excel was used to tally every risk factor studied in each of the 21 papers. This tallying allowed thematic coding to be performed along with the grouping of risk factors into themes of risk factors. For example, many papers mentioned different examples of poor oral hygiene or risk of aspiration (Celis et al., 1988; Stenlund et al., 2017; Rothan-Tondeur et al., 2003; Harkness et al., 1990). These risk factors could therefore be grouped into the theme 'poor oral health/ aspiration risk'. Thematic analysis then allowed the frequency of study and outcomes of the study of this theme to be identified easily (Miles & Huberman, 1994).

The creation of these themes allowed the study to begin answering the research questions by identifying which risk factors were associated with an increased risk of HAP acquisition or mortality (see Table 3). Analysis of these themes could then be done which allowed conclusions to be drawn. These conclusions were regarding the importance of different themes of risk factors, the frequency in which they have been studied and the extent of discrepancies or contradictions in the evidence base.

Further thematic analysis of the papers produced cross-case analysis whereby analysis across cases of risk factor themes was performed. This allowed further information to be drawn from the available literature and added to the ability of this review to answer the research questions. This additional iteration of coding and analysis builds on the scoping review process (Levac et al., 2010) and follows the methodology suggested by Miles and Huberman (1994). A higher order of meta-themes was identified through this additional iteration of analysis and is detailed further in the results section.

#	Author	Year	Study type	Question answered	Study population	Key findings	Type of risk studied	Risk factors identified as associated	Risk factors identified as not associated	Themes associated	Themes not associated
1	Rothan-Tondeur M, et al	2003	Prospective case-control	Determine risk factors and incidence of nosocomial pneumonia.	2142 patients. 75 cases- inpatients aged 65 and older with NP. 1999. USA.	Independent risk factors for NP: history of NP in the last 6 months, oxygen therapy. Additional risk factors: severe malnutrition, cardiac failure, antibiotics in previous month, eating dependency, feeding by nasogastric tube.	Acquisition	NP history O2 therapy	Swallowing disorder, neurological disease, COPD, smoking, steroids, DM, dependency in ADLs, pressure ulcers, flu/ pneumococcus vaccination.	5	3, 1
2	Harkness GA, et al	1990	Epidemiologic case-control	Determine risk factors for nosocomial pneumonia in elderly patients in both acute and long-term care.	60 patients with NP matched to 2 controls each. 1990. USA.	In acute care, best predictors for NP: difficulty with oropharyngeal secretions and presence of a nasogastric tube. In long-term care, best predictors for NP: difficulty with oropharyngeal secretions, deteriorating health, and occurrence of an unusual event. Lung disease, previous infection, previous antibiotic therapy not associated.	Acquisition	In acute setting: Neuro/ renal disease, deteriorating health, reduced GCS, disorientation, dependent feeding, aspiration, difficulty with secretions, NGT.	In acute setting: Suctioning, URTI, confusion, agitation, prev infection, prev antibiotics, prior surgery, lung disease	1, 6, 3, 4	1, 5, 8
3	Stenlund M, et al	2017	Retrospective case-control	Risk factors for HAP in emergency surgery unit.	90 HAP patients, 75 controls. 2008-2013. Sweden.	Aspiration (verified or suspected) was dominant risk factor for HAP. Immobilisation frequently associated with HAP.	Acquisition	Male sex, aspiration, Immobilisation, NG tube, abdominal surgery, gastric retention/ vomiting, COPD, asthma.	Age, GCS	3, 4, 8, 1	2, 3
4	Gomes-Filho I S, et al	2014	Prospective case-control	Periodontitis and NP	315 patients- 85 cases of NP. 2010-2011. Brazil.	People with periodontitis 3 times more likely to get HAP	Acquisition	Periodontitis	N/A	3	
5	Eom C S, et al	2011	Systematic review and meta analysis	Assess evidence of risk from acid-suppressive drugs for pneumonia.	31 studies: five case-control studies, three cohort studies and 23 RCTs. Meta-analysis of the eight observational studies.	H2 receptor antagonist and PPI use may be associated with an increased risk of HAP and CAP.	Acquisition	Anti-acids	N/A	7	

6	Vazquez R, et al	2010	Prospective case-control	Assess predictive power of gurgling sounds during speech or quiet breathing for HAP.	20 cases (patients who gurgle), 60 controls. 2008-2009. USA.	Gurgling sounds heard during speech or quiet breathing are independently associated with HAP. Patients with gurgle more likely to be older and live in nursing homes.	Acquisition	Gurgling sounds	N/A	3	
7	Fortaleza C M, et al	2009	Prospective case control	Risk factors for non-ventilator associated HAP.	66 cases, 66 controls. 2005-2006. Brazil.	Risk factors for HAP: Age, antacid use, Central Nervous System disease.	Acquisition	Age Anti-acids CNS disease	Other comorbidities, invasive procedures/ devices, sedatives, steroids, antimicrobials.	2, 7, 1	1, 8, 3, 5
8	Herzig S J, et al	2009	Prospective cohort	Assess link between acid-suppressive drugs and HAP.	63, 878 admissions, antacids prescribed in 52%. 2219 cases of HAP. 2004-2007. USA.	Significant association for proton-pump inhibitors but not for histamine(2) receptor antagonists. Association stronger for aspiration pneumonia.	Acquisition	PPI use	N/A	7	
9	Scannapieco FA, Bush RB, Paju S	2003	Systematic review	Determine relationship between periodontal diseases or other indicators of poor oral health and initiation or progression of pneumonia (or other lung diseases).	1,688 studies. 21 included: 11 case-control/cohort studies (study population 1,413). 9 RCTs (study population 1,759). 1966- 2002.	Poor oral hygiene and periodontal disease lead to oral colonisation. This is associated with nosocomial pneumonia. Large-scale RCTs needed for further evidence to support provision of oral hygiene procedures to patients that are high risk for nosocomial pneumonia.	Acquisition	Poor oral hygiene	N/A	3	
10	Takano Y, et al	2002	Prospective cohort	Determine prognostic factors in nosocomial pneumonia on general wards.	80 patients. 1996-1998. Japan.	Poor prognostic factors: use of antacids, presence of an ultimately or rapidly fatal underlying condition, presence of 'high-risk' micro-organisms, previous antibiotic use, sepsis, albumin < 3.0 gdl(-1), lactate dehydrogenase > or = 796 IUI(-1), respiratory failure, multiple organ failure, bilateral chest X-ray infiltrates, a Simplified Acute Physiology Score (SAPS) index > or = 11. Multivariate analysis: Factors significantly associated with mortality: presence of an ultimately or rapidly fatal underlying condition. SAPS index > or = 11,	Mortality	Underlying condition, high SAPS index, high LDH.	Age, male sex, smoking, alcohol, comorbidities, surgery, steroids, chemotherapy, shock, coma, WCC>20	1	2, 1, 8

						LDH > or = 796 IUI(-1). On general wards, host factors and disease severity factors are both important prognostic factors in nosocomial pneumonia on.					
11	Feng DY, et al	2019a	Retrospective cohort	Identify factors that affect 30-day mortality of patients with HAP	1158 cases, 150 died within 30 days- these analysed for factors. 2014-2017. China.	Univariate analysis: age >70. DM, COPD. PPI, ETT, alb <30, abx in prev 90 days, ICU admission, lymph <0.8, elevated BUN/alb, MDR pathogens present. Multivariate analysis: PPI, abx in prev 90 days, ICU admission, elevated BUN/Alb, lymph <0.8, MDR pathogens present still associated with 30-day mortality.	Mortality	Multivariate analysis: Prev abx PPI		5, 7	
12	Feng DY et al	2019b	Retrospective cohort	Investigate the epidemiology, microbiology and predictors of 30 day mortality in patients with HAP from gram negative bacteria.	1472 cases of HAP. 2014-2017. China.	Risk factors for mortality were age >70 years, ICU admission, lymphocyte < 0.8, MDR-GNB infection, and elevated BUN	Mortality	Age, ICU admission, low lymphocytes, MDR pathogens, raised BUN	Male sex, smoker, DM, COPD, prev abx, prev tracheostomy, oesophageal intubation, CVC, multilobar infiltration, CRP, WCC, PPI use	2	1, 5, 9, 8, 7
13	Sangmuang , et al	2019	Retrospective cohort study	Determine risk factors for 28-day mortality in patients with hospital acquired pneumonia.	181 cases of HAP. 2013-2016. Thailand.	Factors associated with mortality: duration of treatment, AKI, mechanical ventilation dependency, hematologic disease Age not, other comorbidities not (COPD, CCF, stroke, IHD)	Mortality	Duration of Rx AKI Mechanical vent dependency Haem disease	Age, other comorbidities (COPD, CCF, stroke, IHD), recent antibiotics, ICU admission, LOS >5 days, gender	1	2, 1, 5
14	Mazière S, Couturier P, Gavazzi G	2013	Prospective cohort	Assess relationship between function status and nosocomial infections in the elderly.	223 patients. (All patients >75 admitted in this time eligible). 2007. France.	Factors significantly associated with nosocomial infection included ADL at baseline, ADL at admission, recent functional decline. When functional status at baseline taken into consideration only disability at baseline was independently associated. Disability highest risk factors for nosocomical infections in elderly.	Acquisition	Disability	N/A	4	
15	Zhu J, et al	2015	Retrospective case-control	Investigate relationship between atrial fibrillation and HAP.	8657 patients. 1059 cases, 7598 controls. 2009-2011. China.	AF is an independent risk factor for HAP. Increased risk in HTN, age, heart failure but not smoking, gender, diabetes, congenital or coronary heart disease.	Acquisition	AF HTN Age Heart failure	Smoking, gender, DM, congenital or coronary heart disease	1, 2	1

16	Sopena N, et al	2014	Prospective case-control	Assess the incidence, risk factors and outcomes of HAP in ward patients.	119 cases, 238 controls. 2006-2008. Spain.	Significant risk factors for HAP: malnutrition, Charlson comorbidity index ≥3, previous hospitalisation, reduced consciousness, anaemia, chronic renal failure and thoracic surgery. Complications occurred in 57.1%. Mortality attributed to HAP was 27.7%. Smoking, cancer, DM, chronic heart disease, alcohol not	Acquisition	Malnutrition, comorbidities, previous admission, reduced GCS, anaemia, chronic renal failure, thoracic surgery.	Smoking, cancer, DM, chronic heart disease, alcohol	6, 1, 5, 3, 8.	1
17	Alsuraikh M, Hamdy G	2008	Retrospective cohort	Identify possible causative agents, risk factors, incidence of hospital acquired pneumonia.	132 patients who developed HAP. 1971. Kuwait.	Commonest risk factors: H2-receptor antagonist use (75.8%), smoking (40.2%), diabetes mellitus (39.4%), COPD (38.6%). No difference with age	Acquisition	H2 receptor antagonist Smoking Diabetes COPD	Age	7, 1	2
18	Lee SC, et al	2005	Prospective cohort	Determine risk factors for mortality from NP	132 patients with NP. 1999-2000. Taiwan.	11 risk factors univariately associated, but only 3 after stepwise logistic regression: high 'simplified acute physiology score', inappropriate initial antibiotics, multiple organ failure. Not associated with mortality: age, underlying diseases.	Mortality	High SAPS Inappropriate abx Multiple organ failure	Age Comorbidities		2, 1
19	Gomez J, et al	1995	Retrospective case-control	Assess epidemiological, risk and prognostic factors in patients with NP.	114 cases, 104 controls. 1989-1993. Spain.	Risk factors significantly associated with acquisition: female sex, antibiotic use in prev 6 weeks, admission in prev month and hospital stay over 14 days.	Acquisition Mortality	Acquisition: Female Antibiotics in last 6 weeks Admission in last month LOS >14 days Mortality: Severe underlying disease Initially critical clinical status Steroids Sev/Mod resp failure B/L infiltrates	Acquisition: Age Comorbidities Steroids Mortality: Age Sex Comorbidities Length of stay Admission in last month Antibiotics in last 6 weeks Type of microorganism Type of antibiotic therapy (mono or combination)	Acquisition: 5 Mortality:	Acquisition: 2, 1 Mortality: 2, 1, 5

20	Hanson LC, et al.	1992	Prospective observational/ case control.	Assess risk factors for nosocomial pneumonia in elderly patients. Assess how these may differ from younger patients.	59 cases of NP in >65 year olds. Compared to 59 cases in patients aged 20-50. Elderly cases also matched to elderly controls. 1991. USA.	NP higher incidence in the elderly (RR 2.1). Mortality the same. No significant difference in risk factors. Logistic regression analysis showed that neuromuscular disease, tracheal intubation, low albumin were strong independent risk factors for NP in elderly patients.	Acquisition	Age Intubation In elderly patients: Neuromuscular deficit Intubation Low albumin (poor nutrition)	Not important in this elderly population: Smoking COPD Thoracic surgery	2, 9	1, 8
21	Celis R, et al	1988	Prospective case-control	Assess risk factors and prognostic factors for nosocomial pneumonia.	120 cases of NP, 120 controls over 17 months. 1988. Spain.	Significant predisposing factors: age >70, chronic lung disease, reduced consciousness, tracheal intubation, thoracic or upper abdominal surgery, previous large volume aspiration. Independent poor prognostic factors: Age >60, underlying ultimately or rapidly fatal condition.	Acquisition Mortality	Age Lung disease Reduced GCS Intubation Aspiration Thoracic/abdo surgery. Age Fatal underlying condition, high risk pathogens, bilateral infiltrates, respiratory failure, inappropriate antibiotics	Smoking, prev antibiotics Sex Chronic lung disease Aspiration	Acquisition: 2, 1, 3, 9, 8 Mortality: 2	5 1, 3

Themes:
1= comorbidities, 2= age, 3= oral health/aspiration risk, 4= performance status, 5= previous infection/ admission, 6= recent general deterioration, 7=drugs altering the gastric environment, 8= surgery/ invasive device insertion, 9= recent airway intervention

Table 2. Charting of included papers.

Scoping review stage 5- Collation, summarizing and reporting the results

The next section of the report details the results of the analysis of the included papers that are charted in Table 2. 'Summarising and reporting' forms the fifth part of the scoping review methodology (Levac et al., 2010). The data analysis from the scoping review formed three stages. Firstly, the results of the tallying of risk factors and the emergence and tabulation of risk factor themes identified through thematic analysis. This analysis identified the frequency of research, the importance of different risk factors for HAP acquisition or mortality risk and the discrepancies between papers. Secondly, the cross-case thematic analysis of the papers charted in Table 2 and resulting identification of additional themes describing issues running through the literature. These themes were centred on the issues of discrepancy and variation in methodology.

A discovery of a higher order of themes identified through further analysis took place (Miles & Huberman, 1994). These higher order themes were produced by a further iteration of analysis centred on developing meta-themes as part of the synthesis of the results. These meta-themes included two meta-themes that draw together the original risk factor themes into two higher order themes of risk. A third meta-theme was also produced that describes an observed fracturing of the literature, arising from the identification of discrepancy and variation. These three meta-themes were then used to produce two models. The first model provided a demonstration for how patients are put at an increased risk of HAP acquisition. The second model provided a demonstration of why the literature is fractured.

2.4 Results

The results of the scoping review are reported in the following 3 stages, corresponding to the 3 stages of analysis detailed above:

1) **Risk factor thematic analysis**- risk factor themes produced from coding of charted papers
2) **Cross-case thematic analysis**- further themes identified through coding centred on discrepancy and methodology
3) **Synthesis and emergence of meta-themes**- higher order thematic analysis , production of descriptive models

2.4.1 Risk factor thematic analysis

The review of included papers identified 47 individual risk factors for acquisition of HAP in hospital inpatients and 39 individual risk factors for mortality from HAP. These factors were tabulated and then tallied according to the frequency in which they were reported as per scoping review methodology (Levac et al., 2010). The risk factors for either outcome (acquisition and mortality) were subsequently divided into 9 risk factor themes as seen in Table 3. This coding was based on identifying similar risk factors and grouping them together into themes of risk factor. This was essential to allow comparison between papers in a feasible manner. For example, 'swallowing disorder' (Rothan-Tondeur et al., 2003) and 'difficulty with secretions' (Harkness et al., 1990) (see Table 2) were grouped into the theme of 'poor oral health/ aspiration risk (see Table 3). Table 3 shows the frequency at which each theme was found to be a risk factor for acquisition of HAP, mortality from HAP, or not. Analysis of each of these themes of risk factors was then performed and is detailed below.

Risk factor theme	**Risk for acquisition**		**Risk for mortality**		**Frequency commented on**
	Yes	No	Yes	No	
Comorbidities	7	7	2	6	22
Age	4	3	2	4	13
Poor oral health/ aspiration risk	7 (one systematic review)	3	0	1	11
Performance status	3	0	0	0	3
Previous or recent infection/ admission	3	3	1	3	10
Recent general deterioration	2	0	0	0	2
Drugs altering the gastric environment	4 (one systematic review)	0	1	1	6
Surgery/ invasive device insertion	3	3	0	2	8
Recent airway intervention	2	0	0	1	3

Table 3. Tallying of risk factor theme by frequency in which they were found to be a risk factor.

Comorbidities

The theme of comorbidities was a frequently studied risk factor theme tallied in Table 3. This scoping review highlighted that the presence of comorbidities, either specific diseases or groups of disease (e.g. 'lung disease') was the most commonly studied risk factor for both acquisition and mortality. It was however much more commonly researched as a risk for the former (Rothan-Tondeur et al., 2003; Harkness et al., 1990; Stenlund et al., 2017; Gomes-Filho et al., 2014; Fortaleza et al., 2009; Zhu et al., 2015; Sopena et al., 2014; Alsuraikh et al., 2008; Gomez et al., 1995; Hanson et al., 1992; Celis et al., 1988). Comorbidities were studied in relation to mortality by fewer authors (Takano et al., 2002; Feng et al., 2019b; Sangmuang et al., 2019; Lee et al., 2005; Gomez et al., 1995; Celis et al., 1998). Note, the number of authors did not match the 'number of times studied' as some authors found some comorbidities to be a risk factor and other comorbidities not. This therefore meant that papers were included twice in Table 3- once because they found the theme of comorbidities to be a risk factor and once because they didn't. This issue is discussed further later in the thesis.

Within the literature there were inconsistencies in the reporting of whether the presence of comorbidities is a risk factor for acquisition of HAP, with equal numbers of papers reporting either way. Stenlund et al (2017), Alsuraikh et al (2008), Celis et al (1998) reported that the presence of comorbidities is a risk factor for acquisition of HAP. Rothan-Tondeur et al (2003), Gomez et al (1995), Hanson et al (1992) reported comorbidities are not associated. Finally, Harkness et al (1990), Fortaleza et al (2009), Zhu et al (2015) and Sopena et al (2014) reported both outcomes: that some comorbidities are risk factors but others are not. This meant that seven papers demonstrated that comorbidities are risk factors for HAP acquisition and seven concluded the opposite (see Table 3).

Additionally, papers disagreed as to whether specific diseases (e.g. lung disease) are risk factors. For example, lung disease is reported as a risk factor for acquisition of HAP by Celis et al (1988) and Stenlund et al (2017); however the same disease is found to not be a risk factor for acquisition by Rothan-Tondeur et al (2003) and Harkness et al (1990). Regarding risk of mortality, other papers identify that some comorbidities are risk factors and others not (Sangmuang et al., 2019; Takano et al., 2002). This discrepancy in the literature emerges as a theme in the cross-case analysis of the literature and is discussed later on in the report. Other risk factor themes did not suffer the same issue where individual authors provided evidence that a theme was and was not a risk factor. This was partly a product of the coding system used by the researcher, as explained above.

The review seemed to demonstrate that the relationship between comorbidities and risk of acquisition or mortality from HAP was unclear despite extensive study, especially regarding

acquisition risk (see Table 3). This discrepancy and contradiction was found in the other risk factor themes as well (see Table 3) and is discussed in each individual risk factor theme section below.

Interestingly, there was an absence of systematic reviews or meta-analyses within the evidence-base that studied any comorbidity as a risk factor for either acquisition or mortality.

Age

Age was also a frequently studied factor relating to HAP and the evidence for this risk factor was also contradictory between the charted papers. Regarding acquisition risk, Fortaleza 2009, Zhu 2015, Hanson et al (1992) and Celis et al (1988) all found that age increases the risk of HAP acquisition, whereas Stenlund et al (2017), Alsuraikh et al (2008) and Gomez et al (1995) did not.

Regarding mortality risk, two papers (Feng et al., 2019b; Celis et al., 1998) found that increasing age increases the risk of mortality from HAP. This finding is contradicted by the findings of four papers which showed that increasing age is not associated with an increased mortality risk (Takano et al., 2002; Sangmuang et al., 2019; Lee et al., 2005; Gomez et al., 1995).

Another finding in relation to age is that by Hanson et al (1992) who found that the importance of various risk factors changes with age. This was an interesting point in itself and also may go some way to explain the discrepancies across papers. If the age of the studied population differs, so might the relative importance of different risk factors.

As with comorbidities there were no systematic reviews or meta-analyses studying age as a risk factor for HAP.

Poor oral health/ aspiration risk

Factors included in this theme related to anything that could affect a patient's baseline oral health or aspects that could increase their risk of aspirating. These included poor oral hygiene (Scannapeico et al., 2003), swallowing disorders (Rothan-Tondeur et al., 2003) and reduced consciousness (Harkness et al., 1990; Sopena et al., 2014; Celis et al., 1988).

Poor oral health/ aspiration risk is a frequently studied theme regarding HAP acquisition but there is discrepancy between different papers. Seven papers showed that poor oral health/ aspiration risk is associated with an increased risk of HAP acquisition (Harkness et al., 1990; Stenlund et al., 2017;

Gomes-Filho et al., 2014; Vasquez et al., 2010; Sannapieco et al., 2003). Alongside this, three papers disagreed and showed that this theme is not associated with an increased risk of acquisition (Rothan-Tondeur et al., 2003; Stenlund et al., 2017; Fortaleza et al., 2009).

One of the papers that reported a positive correlation between poor oral health and risk of acquiring a HAP is a systematic review of 21 papers (including 9 randomised control trials (RCTs)) (Scannapieco et al., 2003). This is significant as this paper was of a higher order than others given the type of evidence. This therefore provided much more weight to an argument that poor oral health/ aspiration risk increases HAP acquisition risk. Comparing this paper to others that contradict it on an equal basis is inappropriate. Acknowledging this is important in the context of a scoping review as although the foundation of such a review is not to assess the quality of the evidence it is important to acknowledge it (Levac et al., 2010).

There was only one paper studying poor oral health/ aspiration risk in relation to mortality risk and this paper did not find it to be a risk factor (Celis et al., 1988).

The evidence for poor oral health/ aspiration risk being a risk factor for HAP was therefore convincing. However, as with other risk factor themes, discrepancies within this theme were still present. For example, Stenlund et al (2017) find that a history of aspiration is a risk factor, but reduced Glasgow Coma Scale (GCS) is not. There may therefore be room to contract the theme to one that is more specific. There may be two themes within poor oral health/ aspiration risk, for example one being that of previous aspiration and one for reduced consciousness, as was seen here in the paper by Stenlund et al (2017).

Performance status

Performance status was one of the most poorly researched themes with only three papers being returned from the literature by this scoping review (Harkness et al., 1990; Stenlund et al., 2017; Maziere et al., 2013). Factors included in this theme related to any factor that was related to a person's ability to care for themselves or mobilise. The conclusions drawn from each paper with regard to the relationship between performance status and risk of HAP acquisition were consistent across all 3 papers. The papers all reported that a poor performance status (specifically eating dependency (Harkness et al., 1990), poor functional status (Mazière et al., 2013) and immobility (Stenlund et al., 2017)) are associated with an increased risk of HAP acquisition.

No research into performance status as a risk factor for mortality could be found (see Table 3). Research may exist, but this scoping review did not return any results using rigorous search methods. Further research into this patient characteristic is therefore clearly needed with regard to mortality risk. Any risk factor that has a potential for mitigation is of critical importance to understand better. For example, if immobility is found to increase the risk of mortality from HAP then mobilising patients or intensive physiotherapy may potentially save lives. Mazière et al (2013) called for further prospective research to examine the power of the relationship between disability and nosocomial infections.

Previous or recent infection/ admission

This theme was studied in relation to risk of HAP acquisition in 6 papers. An equal number showed an increased risk of HAP acquisition with previous or recent infection/ admission compared to those that did not. Rothan-Tondeur et al (2003), Sopena et al (2014) and Gomez et al (1995) all found an association whereas Harkness et al (1990), Fortaleza et al (2009) and Celis et al (1988) did not.

The findings regarding mortality risk were more conclusive. Feng et al (2019b), Sangmuang et al (2019) and Gomez et al (1995) all found that previous or recent infection/ admission does not increase the risk of mortality. Feng et al (2019a) did find an association. It seems that on balance, previous or recent infection/ admission are not risk factors for mortality from HAP. The evidence is unclear regarding risk of acquisition. Individual risk factors in this theme showed individual discrepancy, for example 'history of nosocomial pneumonia' being a risk factor for acquisition in one paper (Rothan-Tondeur et al., 2003) but not in another (Harkness et al., 1990). This supported the use of the thematic coding used by the researcher as it demonstrated that the discrepancy was not due to inaccurate or inappropriate coding. This discrepancy is discussed later on in this report as an emergent issue identified in the literature.

Recent general deterioration

This theme was only studied in 2 papers, both of which found that a recent general deterioration is associated with an increased risk of HAP acquisition. Recent malnutrition (Sopena et al., 2014) and deteriorating health (Harkness et al., 1990) were the factors studied. No papers were found that showed that there is no association.

Significantly, no papers studying the relationship between this theme and mortality were found in this review. This lack of research into mortality risk, like seen above with performance status demonstrated a real need for further research into this field.

Drugs altering the gastric environment

Overall, 6 research papers studied the relationship between drugs that alter the gastric environment and HAP acquisition risk (namely histamine-2-receptor antagonists and proton pump inhibitors, or grouped together as anti-acids) (Eom et al., 2011; Fortaleza et al., 2009; Herzig et al., 2009; Alsuraikh et al., 2008).

One of the papers that concluded that H2 receptor antagonists and proton pump inhibitors do increase the risk of HAP acquisition is a systematic review and meta-analysis of 31 studies including 23 RCTs (Eom et al., 2011). The papers included in this systematic review were not returned by any database that was searched in this scoping review, which undermined this strategy. This systematic review provided significant evidence of there being an association between drugs altering the gastric environment and HAP acquisition risk.

Not all of the included papers were of such high evidence quality. It is worth highlighting that one of the papers that showed a positive correlation with risk of HAP acquisition merely found that 75.8% of 132 patients with HAP were prescribed H2-receptor antagonists with no statistical analysis of significance (Alsuraikh et al., 2008). The varying nature of evidence thus produced by this scoping review demonstrated a key, intentional feature of scoping reviews; they allow the inclusion of a wide range of evidence (Levac et al., 2010). The evidence for these drugs as risk factors for acquisition of HAP is therefore substantial, diverse and clear, with all the multitude of paper types finding that they increase the risk.

Regarding risk of mortality from HAP, the two papers charted in this review that study this disagree regarding whether these drugs are risk factors (Feng et al., 2019a; Feng et al., 2019b). This discrepancy was in keeping with the findings of this review regarding other risk themes and disagreement seems to run through almost all evidence surrounding HAP acquisition and mortality risks.

Surgery/ invasive device insertion

This theme included papers studying 'surgery' non-specifically (Harkness et al., 1990; Takano et al., 2002), those mentioning specific forms of surgery (i.e. abdominal (Stenlund et al., 2017) and thoracic (Sopena et al., 2014; Hanson et al., 1992) or both (Celis et al., 1988)) and 'invasive devices' (Fortaleza et al., 2009) or 'central venous catheters' (Feng et al., 2019b).

Such an intervention is found to be associated with HAP acquisition in half of the papers that study this (3 of 6) (Stenlund et al., 2017; Sopena et al., 2014; Celis et al., 1988). Both of the papers studying the relationship between this intervention and mortality risk do not find a positive correlation (Takano et al., 2002; Feng et al., 2019b). It therefore seems that it is unclear whether surgery is a risk factor for acquiring HAP and it would appear that it is not a risk factor for mortality from HAP. This area, like others, requires further research as this scoping review did not find many papers studying this theme.

Recent airway intervention

This theme included recent intubation (Feng et al., 2019b; Hanson et al., 1992; Celis et al., 1988) and tracheostomy (Feng et al., 2019b). It was closely related to the previous theme of surgery/ invasive device insertion and provided clear results; recent airway intervention is a risk factor for HAP acquisition, as found by both papers studying this risk factor (Hanson et al., 1992l; Celis et al., 1988). Recent airway intervention is not shown to be a risk factor for mortality from HAP, as found by the one paper studying this (Feng DY et al., 2019b).

This scoping review did not return many papers studying these factors but this may be partly a result of the fact that the review excluded papers that study critical care patients only. It is however important to identify that perhaps more should be done to research ward patients who have recently spent time on critical care units or had recent surgery.

2.4.2 Cross case thematic analysis

This report now describes the results of further analysis of the included papers charted in Table 2. Several emergent themes were identified through cross case analysis of the 21 included papers. These were: a variable depth of research, discrepancy within themes and variable methodology.

Variable depth of research

This scoping review of the available literature surrounding HAP identified large differences in the frequencies with which different risk factors for both acquisition of HAP and mortality from HAP have been studied so far. Table 3 illustrates these frequencies.

The most frequently studied theme was 'comorbidities'. It was arguably inevitable that this theme came out as the most frequently studied because individual studies often found that some diseases did increase risk whereas other diseases did not. This gave comorbidities a 'double hit' in Table 3. Additionally, the theme of comorbidities encompassed an enormous quantity of factors (i.e. individual diseases), whereas the theme of 'age' clearly did not. However, even when bearing the above in mind it remained true that comorbidities are very well studied as risk factors for acquisition and mortality from HAP. Given the clear significance of comorbidities as a burden on society (disease is the reason healthcare has to exist) it is perhaps unsurprising that 'diseases' feature heavily in research. The discrepancy between papers regarding different diseases as described earlier prevented any refining of this theme because individual diseases were found to be risk factors by some papers but not others. For example, lung disease was reported both as a risk factor for acquisition (Celis et al., 1988), and as not a risk factor (Harkness et al., 1990). This is discussed further in the next section.

Age was also well studied and additionally it was not subject to the same caveat as 'comorbidities'. It did not feature twice in any papers as both a risk factor and not a risk factor for either acquisition or mortality. This meant that the high frequency of research into it as a risk factor for acquisition of HAP and mortality from HAP was of note. As with 'comorbidities', the literature was fractured and different papers concluded differently regarding its status as a risk factor. The third most frequently researched theme was 'poor oral health/ aspiration risk'. This theme joined the other two aforementioned themes as having conflicting evidence for whether it is a risk factor for HAP acquisition and mortality.

The themes that appeared to have the clearer, less conflicting evidence feature in far fewer papers (see Table 3). It may have been that these themes would have more conflicting data if they had been studied more frequently. This scoping review therefore provides clear evidence for a need for further research into the poorly studied themes identified. Of particular note were the themes of performance status and recent general deterioration, whose relationship to mortality risk was not found to have been studied at all.

The papers identified in this review study the risk factors for acquisition of HAP far more commonly than the risk factors for mortality from HAP. This scoping review therefore also provides clear evidence for the need for further research in general into the risk factors for mortality from HAP.

Discrepancy within themes

Table 3 illustrated the discrepancies in the findings of the papers included in this review. There was marked disagreement regarding whether many of the factors identified are risk factors for either acquisition of HAP, mortality from HAP or neither. The table listed the discrepancies within 'themes' of factors that were created to allow identification of risk themes. The discrepancies also existed at the level of individual factors and are therefore not a result of inappropriate grouping of factors by the researcher. Discrepancies existed in all themes apart from 'performance status', 'recent general deterioration' and 'recent intubation or general anaesthetic'. These themes are the three least studied themes in this review.

Stenlund et al (2017) report that the presence of chronic obstructive pulmonary disease (COPD) is a risk factor for acquisition, whereas Rothan-Tondeur et al (2003) report that it isn't. Zhu et al (2015) report that congestive cardiac failure is a risk factor for acquisition, whereas Sopena et al (2014) do not agree. Alsuraikh et al (2008) find that diabetes mellitus is a risk factor for acquisition; Sopena et al (2014) do not. The discrepancies on the theme of comorbidities clearly therefore stem from individual diseases being found to be risk factors by some authors but not others.

It is not just within the theme of comorbidities where there are discrepancies. Gomez et al (1995) report that having antibiotics in the last 6 weeks is a risk factor for acquisition of HAP whereas Celis et al (1988) disagree. Regarding the same risk factor but for mortality risk, Feng DY et al (2019b) find that antibiotics in the last 90 days increase the risk of mortality from HAP whereas Sangmuang et al (2019) find that recent antibiotics do not increase this risk.

This report described earlier the finding by Hanson et al (1992) that different risk factors appear to have variable importance depending on the average age of the population studied. A future review of the available evidence may benefit from taking this into account. However, if reviews become too specific with regard to a population age then clearly any conclusions about patient care would only apply to a narrow section of the population. They would then potentially be less useful for clinicians and other healthcare professionals when applied to care.

Variable methodology

Of the 21 papers included in this review, a majority are prospective case control studies (see Table 2). An important issue that emerged when reviewing the literature was the variable methods by which different papers were assessing and then stating the significance of relationships. The majority of papers use multivariate regression analysis (Vazquez et al., 2010; Herzig et al., 2009; Sopena et al., 2014) (see Table 2), however one paper simply uses percentage incidences with no analysis of significance (Alsuraikh et al., 2008).

In drawing conclusions, different authors would state that a factor is associated with increased risk based on different levels of significance. For example $p=0.05$ (Rothan-Tondeur et al., 2003) and $p<0.05$ (Stenlund et al., 2017), compared to $p<0.001$ (Vazquez et al., 2010; Zhu et al., 2015). Furthermore, different authors use different words for levels of significance in their write-ups. Rothan-Tondeur et al (2003) discuss “independent” and “additional risk factors”, Harkness et al (1990) discuss “best predictors”, Stenlund et al (2017) report on “dominant risk factors". Additionally different authors use the word ‘significant’ in their abstracts without stating the level of significance (Harkness et al., 1990; Herzig et al., 2009; Sopena et al., 2014). These differences may reduce the efficiency or clarity with which healthcare professionals can read multiple papers and compare the findings.

Although the remit of this scoping review (as with any other) was not to assess the quality of the evidence reviewed, another feature of this theme of variable methodology is the variable sample sizes of the studies included. The smallest study population came from a case control study of 20 cases matched to 60 controls (Vazquez et al., 2010) and the largest came from a retrospective case control study of 1059 cases and 7598 controls (Zhu et al., 2015). The tallying of the frequency with which various factors or themes are identified as risk factors for acquisition or mortality in this review does not take this into account. Mitigation of this issue may be required in future analysis to strengthen the evidence for which areas require further research.

2.4.3 Synthesis and the emergence of meta-themes

The analysis of the papers included within the review identified several emergent themes of risk factors, ranging from patient age (Zhu et al., 2015) to recent airway intervention (Celis et al., 1988).

A further iteration of analysis was conducted centred on developing meta-themes as part of the synthesis of the results 'themes' (Miles & Huberman, 1994). This thematic analysis is separate to the identification of the risk factor themes that are listed above. This process involved the thematic analysis of the risk factor themes described earlier to answer the research questions in more detail. Further analysis resulted in the production of a model for HAP acquisition based on the presence and importance of different risk factors identified in this review.

A further iteration of analysis was centred on the additional themes that emerged from the literature regarding 'discrepancy within risk factor themes', 'variable depth of research' and 'variable methodology'. This analysis produced an additional meta-theme and allowed the production of a model for why the literature surrounding HAP is fractured. These meta-themes and the production of the models allowed this scoping review to accurately describe what the current available literature regarding risk of HAP acquisition and mortality shows.

Synthesis: risk factor meta-themes

This scoping review aimed to answer two questions:

1) What is currently known from the existing literature regarding the risk factors for acquisition of HAP?

The overall synthesis of results from the scoping review identified that the least conflicting evidence focused on the themes of 'poor oral health or aspiration', 'performance status', 'recent general deterioration', 'drugs altering the gastric environment' and 'recent intubation/ general anaesthetic'. The presence of these factors seem to increase the risk of patients acquiring HAP (Harkness et al., 1990; Stenlund et al., 2017; Sopena et al., 2014; Eom et al., 2011; Celis 1988). However, none of these themes has been studied at a high frequency, although one of the papers regarding the gastric environment is a large systematic review (Eom et al., 2011). Comorbidities and age, whilst studied more frequently have much less clear relationships to risk of acquisition of HAP with different papers disagreeing regarding whether the themes were risk factors (Stenlund et al., 2017; Alsuraikh et al., 2008; Celis et al., 1998; Zhu et al., 2015; Hanson et al., 1992; Fortaleza et al., 2009) or not (Rothan-Tondeur et al., 2003; Gomez et al., 1995; Hanson et al., 1992).

Based on the themes of risk factors that emerged from the literature, the researcher was able to perform another iteration of thematic analysis and produce two 'meta-themes'. The first meta-themes encompassed the risk factor themes of 'poor oral health or aspiration', 'drugs altering the gastric environment' and 'recent intubation/ general anaesthetic'. It could be phrased as so:

> 'Anything relating to the breakdown of the protective mechanisms that ordinarily reduce the risk of aspirating bacteria into the lungs from the mouth or stomach.'

The second meta-theme encompassed the risk factor themes of 'performance status' and 'recent general deterioration'. It could be phrased as:

> 'Anything relating to a deterioration in a patient's ability to care for themselves or to mobilise.'

These two meta-themes, comprised of their individual risk factor themes, could then be integrated into a model for HAP acquisition. This model is shown in Figure 2 below. This figure provided a method by which to describe how patients who are exposed to different risk factors (potentially all at the same time) have an increased risk of acquiring a HAP. In the future, after further research, this model could be of use in clinical care settings. It could act to prompt clinicians and help in the design of systems to mitigate the risk of HAP acquisition for hospital inpatients. Prior to this, the model would need further research via larger studies. This thesis thus acts as a pilot or feasibility study and guides future research to inform practice changes.

2) What is currently known from the existing literature regarding the risk factors for mortality from HAP?

The scoping review struggled to identify any factors or themes of factors that increase the risk of mortality from HAP. Some of the themes seem to not be risk factors for mortality from HAP, namely comorbidities (Feng et al., 2019b), previous or recent infection/ admission (Sangmuang et al., 2019) and surgery (Takano et al., 2002). However these themes have conflicting data regarding this (Harkness et al., 1990; Feng et al., 2019a).

Outside of the scope of this review, but nonetheless of note was the observation that some studies look at individual physiological parameters as risk factors for mortality. For examples the presence of low lymphocytes, (Takano et al., 2002), a high 'simplified acute physiology score' (Lee et al., 2004) or severe respiratory failure (Gomez et al., 1995). These issues are markers of disease severity and not risk factors in the same sense as others. One purpose of this thesis is to identify areas where

interventions may be possible, and so ‘risk factors’ in this thesis refers to modifiable characteristics, not markers of disease severity.

This review did not identify any papers studying the relationship between performance status or recent general deterioration and mortality risk. Due to the paucity of evidence surrounding the issue of mortality risk the researcher was unable to produce a model for mortality from HAP based on the findings of the scoping review. Further research was urgently needed to allow such a model to be produced.

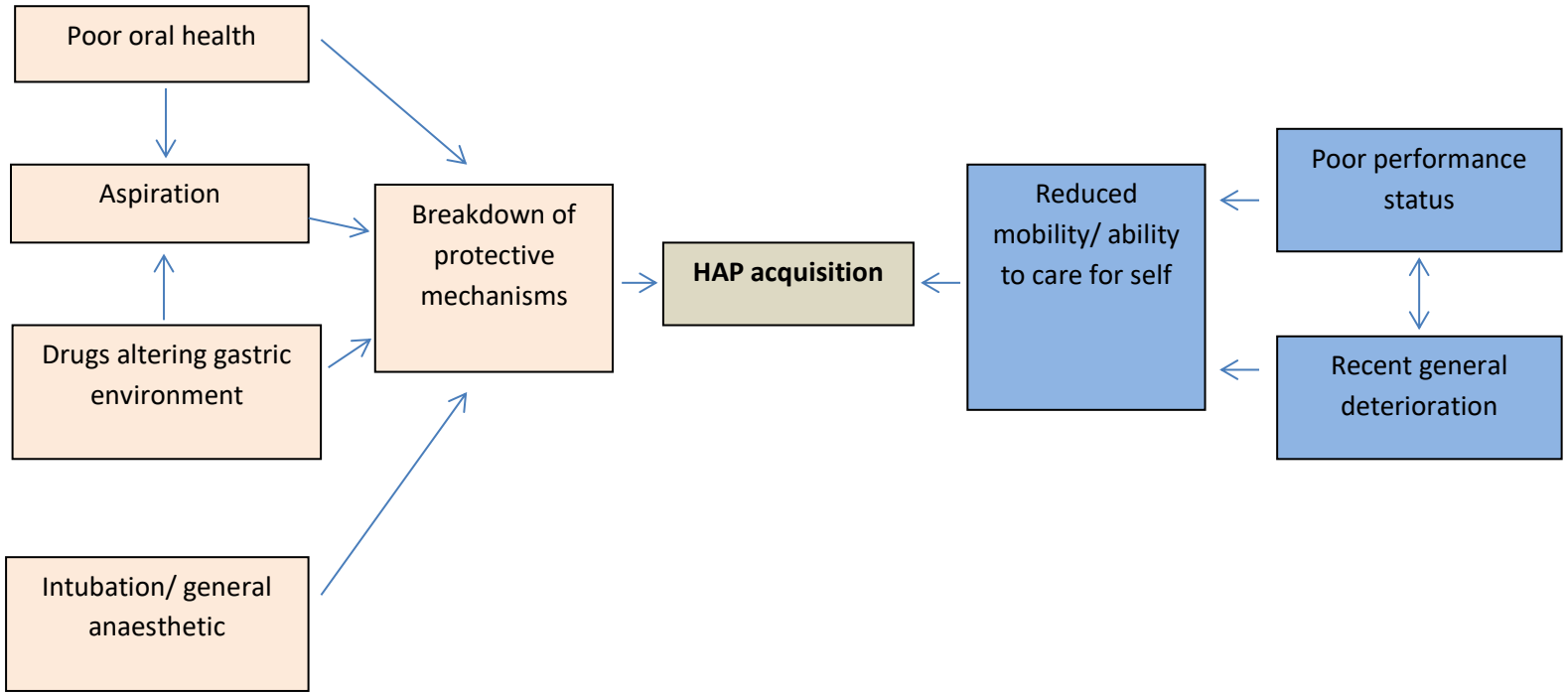


Figure 2. A model for how patients are put at risk of acquiring HAP.

Synthesis: fractured literature meta-theme

An additional way in which this review answered the two research questions was by identifying additional issues surrounding the literature regarding HAP acquisition and mortality. The research questions were as follows:

1) What is currently known from the existing literature regarding the risk factors for acquisition of HAP?
2) What is currently known from the existing literature regarding the risk factors for mortality from HAP?

The additional issues discovered in answering the above questions were discovered to run as themes throughout the available literature. Analysis of these themes allowed the synthesis of an additional meta-theme. This meta-theme also provided an answer to the two questions above.

The section of the report above describing the risk factor meta-themes gave examples of the discrepancies within the available literature surrounding HAP acquisition and mortality. For example, the relationship between comorbidities and age and risk of acquisition of HAP or mortality from HAP was unclear. Different papers disagree regarding whether the themes are risk factors (Stenlund et al., 2017; Celis et al., 1988) or not (Takano et al., 2002).

Further to this theme of 'discrepancy within risk factor themes', other themes running through the literature with regard to clarity were unveiled by this review. 'Variable depth of research' and 'variable methodology' both emerged as important issues within the literature. Referenced examples of these are listed above in the results section.

These three themes: 'discrepancy within risk factor themes', 'variable depth of research' and 'variable methodology' could be combined to produce an additional meta-theme that emerged from the literature. This was the meta-theme of a fractured literature.

Synthesis of this meta-theme allowed the production of a model to represent how the literature has become fractured (Figure 3). This is an important model as it demonstrates how future research could avoid adding to the fracturing of the literature. The model also identified the areas where future research could help to mitigate the fracturing that already exists.

In summation, an additional answer to the two research questions had been produced: The existing literature regarding risk factors for both acquisition and mortality is extremely fractured.

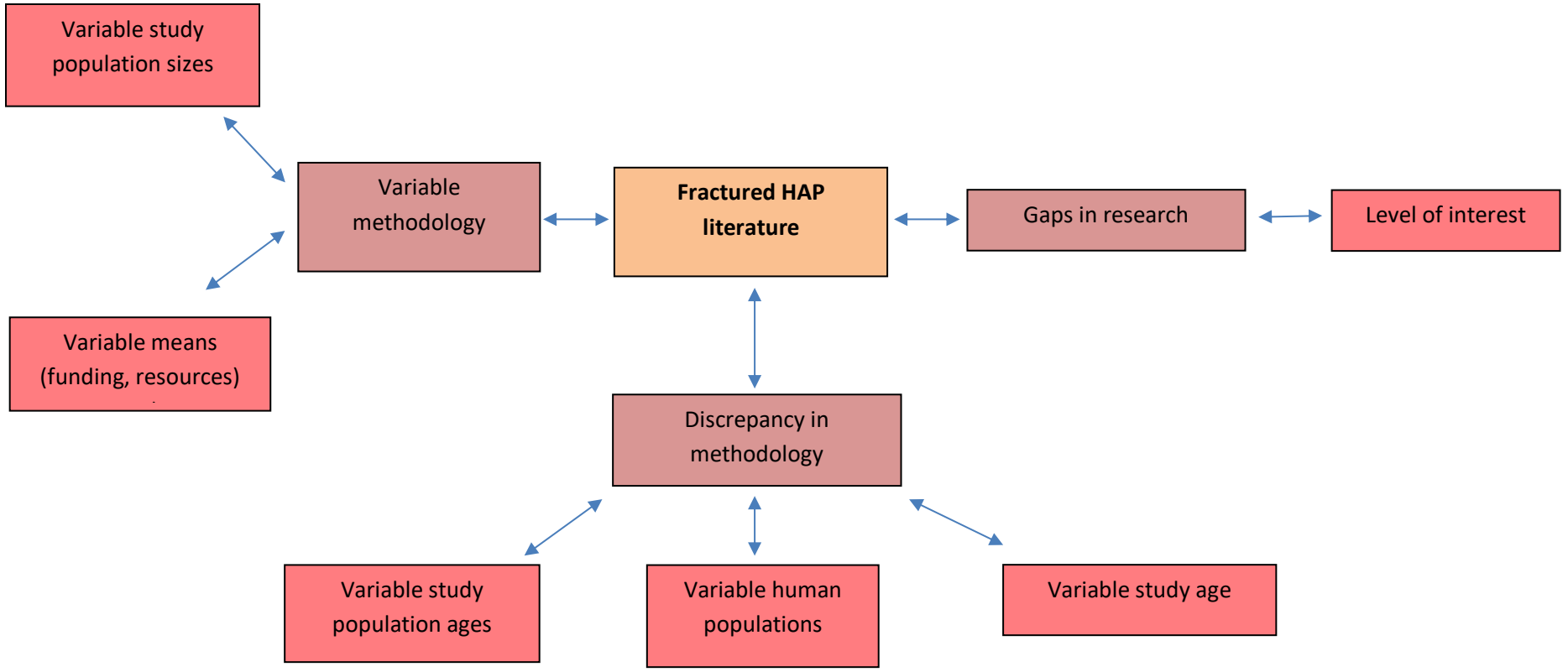


Figure 3. A model describing how the literature surrounding HAP has become fractured.

2.4.4 Results summary

This scoping review answered both of the research questions twofold. It identified which factors (if any) appear to be risk factors for acquisition of HAP and mortality from HAP. It has also identified that the literature regarding both risks is fractured.

The review discovered that the factors that increase the risk of acquiring HAP form two broad areas or meta-themes. Firstly, any factors that result in a breakdown of the protective mechanisms that ordinarily reduce the risk of aspirating bacteria into the lungs from the mouth or stomach. Secondly, any factors relating to a deterioration in a patient's ability to care for themselves or to mobilise. These two meta-themes were used to produce a novel model describing how the risk of HAP acquisition can be increased for hospital inpatients.

The review also allowed the production of a model for why the literature surrounding HAP acquisition and mortality is fractured. This model describes how this fracturing occurs based on multiple issues surrounding clinical research.

2.5 Discussion

HAP is a common disease that is poorly studied outside of intensive care units. It affects 8-10% of patients admitted to elderly care units (Burton et al., 2016) and is associated with increased risk of morbidity and mortality in affected patients. It also results in increased length of stay in hospital and likelihood of discharge to a nursing home (Sopena et al., 2014). HAP is a form of nosocomial infection, a group of diseases that impart enormous burden on societies and healthcare systems across the globe (WHO 2011). The mitigation of HAP and all nosocomial infections is therefore clearly of great importance.

The risk factors for both acquisition of HAP and mortality from HAP were identified by the researcher as clearly of importance to understand better. In undertaking this scoping review the researcher aimed to do this by answering the following two questions:

1) What is currently known from the existing literature regarding the risk factors for acquisition of HAP?
2) What is currently known from the existing literature regarding the risk factors for mortality from HAP?

In answering these two questions this scoping review studied the literature surrounding the risk of HAP acquisition and mortality and identified three meta-themes underpinning the evidence base. These three meta-themes were used to produce two models. The findings of this review and the models produced added to the current literature surrounding HAP by reporting novel findings and providing novel descriptions of the data. This report now discusses the significance of these outcomes in the context of the current literature and global scientific opinion.

Discussion: risk factor meta-themes and modelling

This scoping review produced a model demonstrating how the risk of HAP acquisition is increased for hospital inpatients. This model was underpinned by the two emergent meta-themes that were found in the literature. It is known that the mechanism by which HAP forms is the aspiration of oropharyngeal matter. Therefore, the findings of this review of an increased risk of acquisition from anything that makes this more likely (one meta-theme) were in keeping with the current understanding of HAP aetiology (Ewan et al., 2017).

The model of HAP acquisition represented how some of the risk factor themes seen in Table 3, (comprised of the individual risk factors charted in Table 2) could be combined together to form risk

factor meta-themes. These meta-themes then either unilaterally or through combination increased the risk of HAP acquisition. The presence of any of the risk factor themes found to be associated with HAP acquisition, and therefore either of the risk factor meta-themes, appeared to increase the risk of HAP acquisition. The model in Figure 2 demonstrated this relationship.

Many of the risk factor themes were related to each other. For example, a patient with a recent general deterioration would likely have had reduced performance status. There may therefore be relationships across the two sides of the model as well. The increased risk of aspiration of oropharyngeal matter formed an important part of the model for HAP acquisition produced by this review, and was in keeping with the literature regarding the pathology behind HAP (Ewan et al., 2017). The researcher wondered if the association between HAP acquisition and the other meta-theme of recent general deterioration or reduced mobility may be due to this meta-theme actually being a proxy for the other. It may have been a sign that someone is generally weaker and therefore more likely to have the features of the other meta-theme i.e. weaker defensive mechanisms. The findings regarding mobility were in keeping with other findings in the wider literature. It has previously been shown that the initiation of an 'Early Mobility Bundle' reduced the incidence of HAP in medical inpatients (Stolbrink et al., 2014). There therefore appears to be a link between mobility (or lack thereof) and HAP incidence.

The risk of mortality from HAP did not overall seem associated with any of the identified themes that were studied. Factors that were found to be associated were contradicted in other papers to an equal or greater degree. There were obvious gaps in the literature regarding risks for mortality from HAP. No papers were identified studying the relationship between performance status or general deterioration and mortality from HAP. This may mean that potential areas suitable to intervention like the 'early mobility bundle' (Stolbrink et al., 2014) mentioned above are being missed. Poor performance status has previously been shown to be an independent risk factor for severe illness and mortality from community acquired pneumonia (Ishiguro et al., 2016).

Identification of risk factors for mortality from HAP through further research would allow the production of a model similar to that which this review produced for HAP acquisition. Attention is particularly needed on the risk factor themes of poor performance status and general deterioration. The production of such a model could aid clinicians in the care they provide to patients. It could help by identifying the important areas where suitable interventions such as the 'early mobility bundle' mentioned above (Stolbrink et al., 2014) could be instigated.

Discussion: fracturing meta-theme and modelling

The scoping review discovered that the literature surrounding HAP acquisition and mortality risk is fractured. Different papers disagree on what is a risk factor for acquisition or mortality from HAP (see Table 3). They also disagree on the significance of these relationships and differ in how this is both identified and reported. Furthermore, there are large gaps in the literature in potentially important issues surrounding mortality.

To the researcher's knowledge, this fracturing has not been formally identified and reported in this manner before. This scoping review therefore further added novel insight to the available literature and scientific understanding regarding HAP.

Additional factors that add to the fracturing of the literature included the fact that the papers studied in this scoping review involve variable methodologies. This was due to the inevitable feature of research of different researchers having different means available to them with which to conduct their work. Different budgets allow for different study sizes and methodology. The variable population sizes were both a cause and consequence of a variable methodology. Methods varied from systematic reviews (Eom et al., 2011), through prospective case control and cohort studies both small (Celis et al., 1988) and large (Herzig et al., 2009) to large retrospective case-controls (Zhu et al., 2015) and small retrospective cohorts (Sangmuang et al., 2019).

Different researchers also have differing aims and objectives with their work, and therefore have different interests that they wish to study. This results in gaps forming in the research where one area may, either by chance or by other pressures (e.g. funding), become less well researched compared to others.

As mentioned above, Hanson et al (1992) found that different risk factors had variable importance at different ages. Studies performed on populations with different average ages may therefore have different findings. However, factors should be adjusted for to mitigate the impact of this issue. Additionally, the papers studied in this review come from across the entire planet. The different papers that were compared were therefore often studying different human populations. Papers originated from countries such as Sweden (Stenlund et al., 2017), Japan (Takano et al., 2002), Brazil (Gomes-Filho et al., 2014), Thailand (Sangmuang et al., 2019), USA (Harkness et al., 1990) and France (Maziere et al., 2013). Aetiologies, pathogenesis, sociological or environmental factors may all have been different in these populations. Discrepancies were therefore highly likely and any attempt to remove this issue would have rendered the results only applicable to one group. This may be

necessary, but many hospitals look after people of multiple ethnic backgrounds and therefore need knowledge applicable to the masses whenever possible.

One additional issue leading to discrepancy is the variable age of the studies looked at. Excluding the systematic review by Scannapieco et al (2003) the studies investigated populations from 1990 to 2017 (the systematic review included one paper from 1966) (see Table 2). Although 27 years is not a huge span of time it is likely that practice had changed several times over this period with the issuing of successive clinical guidelines. This change of practice may have meant that the relative importance of different risk factors changed over time. This fact clouds the evidence further.

This scoping review highlights the need for urgent further research into the area of HAP acquisition, and to an even greater degree HAP mortality. High quality research using standardised methods of conduction and reporting will provide clarity to this muddy field of contradictory research. This may include systematic reviews and meta-analyses of the literature as well as novel empirical research. This is of vital important to aid clinicians and other healthcare professionals in the care they provide for their patients.

Pilot studies of novel areas should be considered to help guide this initial empirical research. The model produced by this scoping review provides clues as to how the fracturing of the literature could be mitigated and is therefore a useful resource for the planning of these future pilot studies.

Discussion- strengths and limitations

This scoping review identified novel information regarding what is known regarding risk factors for HAP acquisition and mortality. The review utilised a strict methodological framework accepted by the scientific community. This method of scoping review is thought to be appropriate in the context of seeking to analytically interpret the literature as in this case (Levac et al., 2010). Scoping reviews have previously been shown to be useful for identifying a need for further research, specifically systematic reviews (Tricco et al., 2016). This was demonstrated to indeed be true in this scoping review, where a need for clarity and systematic synthesis has been identified. Whilst full quality appraisal of the included papers was not conducted, this review applied critical appraisal techniques and discussed these issues within the analysis and discussion. This critical appraisal is an additional part of the methodological framework and Daudt et al (2013) called for its use to increase the utility of scoping reviews.

This review identified both themes and meta-themes based on coding and thematic analysis that were conducted according to accepted and proven methodology (Miles & Huberman, 1994). This methodology allowed the researcher to understand the literature and develop a synthesis that allowed the reader to easily visualise and contextualise the issues.

There were of course some limitations to this review. The fact that the review is a scoping review brings strengths regarding the breadth of information gathered. However, despite quality appraisal methods being utilised as mentioned above, this form of literature review does not employ rigorous quality appraisal. It is therefore possible that poorly conducted research impacts on any conclusions that can be made. This limitation is applicable to all scoping reviews and was not therefore an error of this specific research but rather undermines all scoping reviews. It is a consequence of one of the main objectives of a scoping review; the aim to provide a narrative of a broad range of literature and identify gaps (Levac 2010). Quality appraisal methods were utilised throughout and are clearly stated in this report, aiding the reader to identify this potential issue.

An additional limitation stems from the methods used to analyse the data. More detailed qualitative analysis may be possible, although the nature of the papers reviewed would limit this. The papers included in this review all reported quantitative data regarding different risk factors, utilising statistical methods such as adjusted odds ratios (Eom et al., 2011), unadjusted odds ratios (Gomes-Filho et al., 2014) and multivariate logistic regression (Sopena et al., 2014). Qualitative analysis of these data is much less appropriate than, for example interview transcripts, and must be analysed using coding and thematic analysis.

2.6 Conclusion

This scoping review provides novel insights into the understanding of risk factors for HAP acquisition and mortality. It identifies that risk factors for acquisition of HAP can be placed into two meta-themes. The first of these include any factor that increases the risk of a breakdown of the protective mechanisms that stop aspiration of oral flora. The second includes anything that increases the risk of a loss of performance status or mobility. As discussed above, the review suggests that the second of these meta-themes may be a proxy for the first.

The review also identifies a third meta-theme of a fractured literature. One outcome of this fracturing is that there is very little evidence regarding risk factors for mortality from HAP, and that much more research is urgently needed. The literature surrounding risk factors for acquisition is full of contradictory findings and conclusions, and there is huge variation in the frequency with which factors were researched.

Synthesis of these three meta-themes resulted in the production of two models. The first model demonstrates how different risk factors combine and lead to an increased risk of HAP acquisition. The second model demonstrates why the literature surrounding risk factors for HAP acquisition and mortality is fractured.

This synthesis demonstrated why further standardised, well-conducted and well reported research into these risk factors are urgently needed to improve clarity within the fractured literature. This would allow refinement of the first model and the production of a similar model for mortality risk factors. These models could then help healthcare professionals to care for their patients and reduce the frequency and thus impact of this important nosocomial infection.

Systematic reviews into this field are also potentially of great value to further improve understanding and guide future research. Such research could further inform the degree and reason for literature fracturing and inform the modelling of HAP acquisition.

This scoping review suggests that the greatest current need and therefore first stage in reducing the fracturing and improving the models should be pilot studies into the relationship between understudied risk factors and HAP mortality. Pilot studies will guide researchers towards the most important risk factors and guide the best methodological approach for such research. This scoping review identified the most pressing issues. In particular, the issues of performance status and general decline must be studied, and clarity brought to issues of age and comorbidities.

Chapter Three

Hospital Acquired Pneumonia: an exploratory study

3.0 Introduction

The aim of the exploratory pilot study detailed within this chapter, informed by the work done in Chapter Two, was to explore the subject of frailty within the context of HAP. More specifically, the study aimed to discover if frailty affected how patients with HAP present, and whether frailty affected mortality risk from HAP.

3.1 Background

The scoping review detailed in Chapter Two of this thesis identified several important novel findings regarding HAP. Through repeated iterations of thematic analysis (Miles & Huberman, 1994) the review discovered emergent themes that described the evidence regarding risk factors for acquisition of HAP and mortality from HAP. The summation and synthesis of these findings resulted in the identification of three meta-themes. These included two meta-themes of risk factors that increased the risk of HAP acquisition and one meta-theme of the fractured literature surrounding HAP.

The identification of these emergent themes and meta-themes allowed the production of two models. One model demonstrated how risk factors could lead to a patient having an increased risk of acquiring a HAP (Figure 2), and the other demonstrated how the literature surrounding HAP had become fractured (Figure 3).

The scoping review in Chapter Two identified that there was very little evidence regarding risk factors for mortality from HAP in the available literature. There was insufficient evidence to produce

a meta-theme through thematic analysis or produce a model describing this risk factor in the same way as was possible for acquisition risk. Due to this, there was therefore an urgent need for more research into the risk factors for mortality from HAP, particularly performance status and general deterioration (given their paucity of research). It was suggested at the end of Chapter Two that this should begin with pilot studies into under-studied areas in order to inform future research. It was hoped that this would add information and clarity to the evidence base, thus increasing the scientific community's ability to produce similar models for HAP mortality risk. It was also proposed that this could reduce the fractured nature of the literature.

The scoping review in Chapter Two identified contradictory evidence for comorbidities, age, performance status and general deterioration as risk factors for acquisition and mortality from HAP (Feng et al., 2019 (2), Zhu et al., 2015, Gomez et al., 1995, Lee et al., 2005; Mazière et al., 2013). There was also a paucity of evidence regarding general deterioration and performance status and risk of mortality with no papers being returned that studied those factors. It was clear to the researcher that an individual with poor health at a young age may be at a higher risk than a healthier person at an older age. Variation and confounding of these factors could therefore have gone some way to explain the discrepancy in results regarding comorbidities, age and general deterioration. The researcher therefore proposed that a more accurate proxy of risk, taking into account age, comorbidities, performance status and general deterioration could be frailty, as is explained below.

Frailty is defined as a clinical condition that results from a decline in physiological reserve with age. It manifests as a vulnerability to change in health due to minor insults from illness or injury and has been deemed to be the most problematic consequence of an ageing population (Clegg et al., 2013). Frailty is associated with many chronic diseases including respiratory and cardiovascular disease and it is more common if two or more diseases are present (Fried et al., 2001). Whilst it is a separate and distinct entity to age, comorbidity, disability and performance status it is known to be closely related to these issues (Clegg et al., 2013; Fried et al., 2001; Hoogendijk et al., 2019; Mitnitski et al., 2001). Frailty increases the risk of many adverse outcomes, including falls, delirium, hospitalisation and death (Clegg et al., 2013; Fried et al., 2001).

The frailty syndrome is a consequence of age, comorbidities, performance status and general deterioration (Clegg et al., 2013; Fried et al., 2001; Hoogendijk et al., 2019; Mitnitski et al., 2001). These factors all have either contradictory evidence or paucity of evidence regarding their relationships with HAP mortality risk (Feng et al., 2019 (2), Zhu et al., 2015, Gomez et al., 1995, Lee et al., 2005; Mazière et al., 2013). The researcher therefore chose to study frailty in this Chapter because they wondered whether this patient factor, which is effectively a 'sum of the above issues'

may have had a clearer relationship with HAP mortality risk. For example, as mentioned above, a very elderly person who had few comorbidities or a good performance status may have a similar frailty to a younger person with many comorbidities and a poor performance status. These two patients may therefore have a similar risk of HAP mortality, despite their ages being very different. This concept of frailty score being of utility in assessing negative outcome has been explored many times before. A very recent scoping review performed since the work of this thesis began has since demonstrated this. This scoping review published in 2020 summarises how frailty scoring has been studied many times in regard to multiple different outcomes and has real utility in the care of elderly populations (Church, et al., 2020). The most common of these outcomes that has been studied in the past is mortality; here, frailty score (in this case the clinical frailty scale) has been shown to be predictive in 87% of included studies. The scoping review also demonstrated that frailty score was associated with 'complications' in 100% of studies, comorbidities in 73%, length of stay in 75% and falls in 71%.

The scoping review in Chapter Two did not find any papers studying frailty in the context of HAP; nor did the scoping review by Church et al (2020). Further research into the issue of frailty in this context, and more specifically as a risk factor for mortality from HAP was urgently needed. The researcher hypothesised that it may be the combination overall of the risk factor themes of comorbidities, performance status, age and recent general deterioration that was associated with risk of HAP mortality. The interaction between these factors within the frailty syndrome may cloud their individual relationships with the outcome of HAP mortality. If frailty takes into account multiple issues (Fried et al., 2001; Hoogendijk et al., 2019; Mitnitski et al., 2001) which have contradictory evidence in their role as risk factors then by studying frailty it may be possible to gain clarity regarding individual risk of mortality from HAP. It was hoped that in assessing frailty, this thesis could begin to improve the clarity within the literature, as well as add to a model for HAP mortality risk.

This chapter contains a piece of empirical research that aimed to begin study into the above issues. In addition to studying the relationship between frailty and mortality risk the study aimed to discover more about the effect frailty had on how patients with HAP present and progress with their illness. The researcher hoped that the study of these issues would add further useful information to the evidence base and aid healthcare professionals in the care they provide for their patients.

3.2 Aims and Objectives

The empirical research in this chapter was conducted in response to the conclusions of Chapter Two of this thesis. The scoping review identified the need for further pilot studies into risk factors for mortality from HAP. The risk factor of interest, frailty, was chosen based on the findings of the scoping review, which highlighted a paucity of evidence and a discrepancy regarding certain risk factors for mortality. The hope was that frailty may help to bring together multiple issues and act as a more accurate representation. Frailty was also an issue of interest to the researcher from previous clinical and academic work.

The aim of this exploratory pilot study was therefore to assess the relationship between frailty score and the risk of mortality from HAP in hospital inpatients outside of the intensive care unit. This study also investigated any association frailty had with how these patients presented with HAP. For example, how frailty score correlated with time from admission to diagnosis, observations at time of diagnosis, and blood tests. Assessing the significance of these associations could then inform the likelihood of a causative effect.

The study hypothesis was that an increasing frailty score would be associated with the following:

1. An increased risk of mortality from HAP
2. A lower early warning score
3. A smaller rise in inflammatory markers

Through studying frailty within this context of HAP, the overarching aim of the study was to add detail and clarity to the evidence base surrounding HAPs and frailty. In doing this it aimed to help healthcare professionals care for patients with HAP, frailty or both.

Within this thesis, ‘early warning score’ refers to the system used throughout the NHS to highlight patients who are likely to deteriorate and become more unwell (Subbe et al., 2001). More detail is given regarding it later on in the thesis. When referring to ‘inflammatory markers’, the researcher is describing the results of tests done to measure the level of inflammation in a person, which can be due to infection. Such tests are used within the NHS and other healthcare systems to provide evidence of this. More specifically these are the markers ‘white cell count’ and ‘C-reactive protein’, both of which can be raised in an infection such as HAP.

Mortality was measured at 7 and 30 days after diagnosis of HAP, a common approach within healthcare research and monitoring outcomes (Hsieh et al., 2021; Nersesjan et al., 2020).

3.3 Approach and Methods

Study design

The approach adopted to allow the researcher to test the above hypotheses was an overarching case study design as first proposed by Yin (2014). This form of approach focuses on detailed study of either a single case or a small number of cases. It focuses on observational data and can provide insight into a wider situation or population (Yin, 2014).

This study aimed to investigate a small number of HAP cases. Using observational data it aimed to explore the issue of frailty within the context of HAPs and thus provide insight into the wider issues of both HAPs and frailty. A case study approach is focused and made up of multiple different levels of analysis. The key feature is that it consists of analysis both across cases and within cases (Yin, 2014). For the research within this chapter, individual cases of HAP incidents formed a larger case of a season of HAPs over a set period of time. The approach mandated individual cases to be studied alongside the larger case series of the season of HAPs as an entity itself. Analysis and comparison allowed the researcher to shed light on the wider issue and allowed detailed study of frailty in the context of HAP.

Case study work is characterised by its use of a variety of research methodologies; quantitative, qualitative and mixed methods designs can all be utilised in assessing single and multiple cases. The study design proposed by Yin (2014) provides a flexible framework for mixed-methods design to guide researchers. The framework thus enables a quantitative analysis of data whilst simultaneously allowing a focus on a qualitative understanding of the 'case' across multiple or single settings.

Different types of case study work exist and have been performed over the years. The different methodologies underpinning these are summarised by Yin (2014) in a matrix which can be seen in Figure 4. Options available within case study work are single or multiple case designs. These options are then differentiated as either holistic or embedded. This depends on the units of analysis, which may be at one or a number of levels respectively (Figure 4).

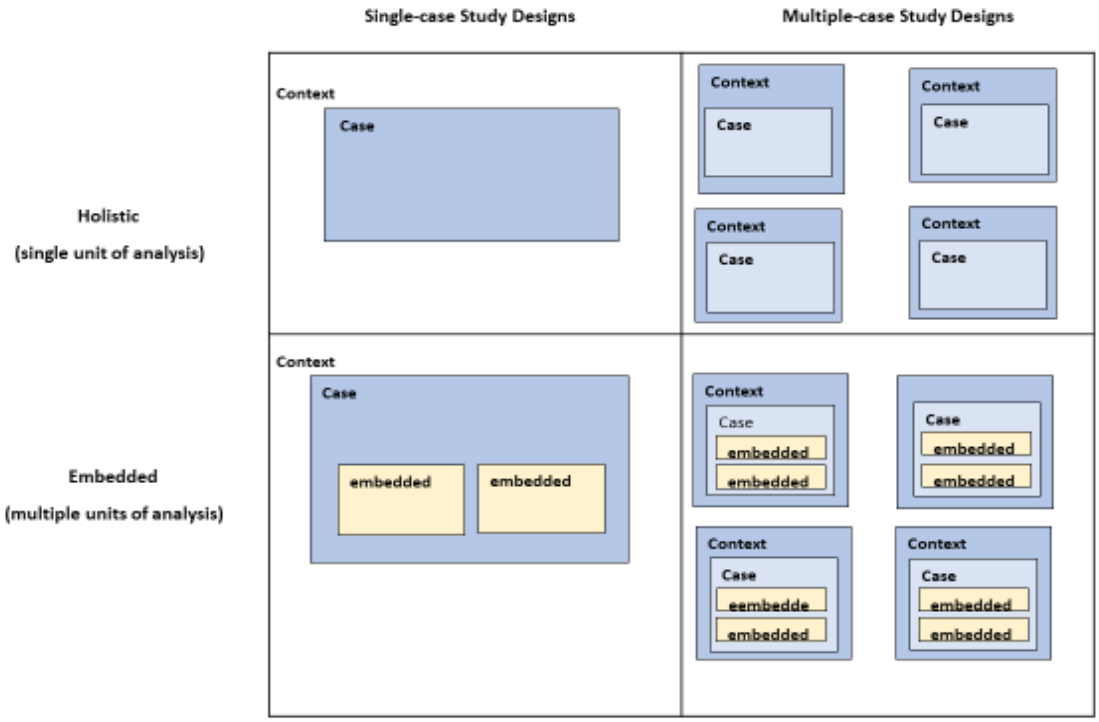


Figure 4. Case study types (adapted from Yin, 2014).

The study in this Chapter utilised an exploratory case study design (Yin, 2014). Of the types detailed in the above matrix this study consisted of a single case and embedded type (Yin, 2014). The study in this chapter consisted of documentary analysis of multiple cases of HAP through interrogation of single units of clinical case notes data. This was all performed within the wider context of a HAP season, with all collected HAP cases forming the larger case of the HAP season that year. Data collection of case notes data was not contemporaneous and the documentary design renders this study outside of temporal definitions; it is neither retrospective nor prospective.

Sampling and recruitment

In total 37 patients were included in this study from two medical wards (one respiratory/ general medicine and one geriatric/ general medicine) at a district general hospital (DGH) in Bangor, North Wales, United Kingdom.

All patients on the two wards who had been diagnosed with HAP between October 2019 and March 2020 inclusive were included in the study.

This study comprised documentary analysis of a case of 37 patients (individual cases) who have been cared for on these wards over a specific period of time. The time period chosen was known to have a higher incidence of HAPs from clinical experience of the researcher. No patient care was affected or modified in any way by any data collection.

The diagnosis of HAP was made according to National Institute for Health and Care Excellent (NICE) guidelines of a pneumonia occurring at least 48 hours after admission to hospital and not incubating at time of admission (NICE, 2020). Exclusion criteria were as follows: patients who had a previously diagnosed community acquired pneumonia (CAP) at time of diagnosis of HAP, patients who had spent any time on intensive care and patients diagnosed with covid-19. Data collection was halted as soon as the coronavirus pandemic arrived elsewhere in the hospital to prevent it acting as a confounding factor.

Regarding the use of a chest x-ray (CXR) in the diagnosis of HAP, this study included all patients treated for HAP within the time period. NICE guidelines describe the diagnosis of pneumonia being 'supported' by the use of a CXR. Table 4 shows the baseline characteristics of the studied sample. Of these 37, 9 did not have CXR changes in keeping with HAP. After consideration it was decided to include these cases as they received the same management in the hospital being treated as a clinical diagnosis of HAP. This phenomenon of a 'hospital acquired lower respiratory tract infection' ('HALRTI') is an important one to mention. It is the personal clinical experience of the researcher that patients are often treated for HAP without CXR changes and treatment proceeds on the basis of this 'HALRTI' phenomenon. This study therefore better represents 'real-world' practice by including these cases. The researcher considers that this is therefore of more use to practicing clinicians.

Data collection

Data collection was performed by examining case notes both retrospectively (n=21) and prospectively (n=16) from the point of starting data collection in January 2020. As the study was not interested in any temporal relationships comparing the two data sets these data were then grouped together to form the final data set.

Data from both wards were combined to form the case set of HAPs, with each individual HAP case being available for analysis within. All data were numerical, with most being continuous data (observations, blood tests) but some were ordinal (frailty score). All data were collected by the researcher and an additional co-researcher who was collecting the same data for a different study.

The process for prospective data collection was as follows: patients on both wards diagnosed with HAP were identified by the treating team and the researchers were informed. The researchers could then examine the medical case notes and extract data from both before and after the diagnosis, as per the research questions.

Data were often collected in two stages as the admission data and data from the time of diagnosis were available immediately. However, the data regarding mortality had to be collected later, at 7 and 30 days after initial diagnosis. The prospective cases (and some retrospective cases) were therefore followed up.

The process of data collection for the retrospective cases was as follows: the researchers studied doctors' 'ward lists' (accurate summaries of patient diagnoses for each day on a ward) to identify diagnoses of HAP as far back as October 2019. These notes were then requested from medical records and all data could be collected in one sitting for this HAP case. Those close to January were also followed up to collect data on 7 and 30 day mortality if necessary.

All HAP cases from both wards from both retrospective and prospective data collection were combined into the case set of HAPs. In summary, the sources of patient information were as follows: paper case notes, electronic records of laboratory and radiological reports and discharge letters. The baseline characteristics of the included 39 HAP cases are represented in Table 4 and the characteristics at time of diagnosis in Table 5. Data collected from electronic records came from the 'Welsh Clinical Portal' system by the researcher and one other principle researcher. Frailty scores were extracted from the case notes where documented as close to time of diagnosis as possible. The researchers did not interpret any laboratory, radiological or clinical data themselves and only recorded data from patients who the treating team had decided were suffering from a HAP.

Data analysis

All data were initially anonymised and recorded onto Microsoft Excel before being transferred into SPSS version 25 for analysis. Spearman's rank correlation coefficients were calculated for all relationships studied (frailty score and time from admission to diagnosis, early warning score (EWS), respiratory rate, heart rate, systolic blood pressure, temperature, diastolic blood pressure, white cell count, C- reactive protein; all at time of diagnosis). These values can be seen in Table 6 and are described in the results section. Spearman's rank correlation was chosen as the analysis method due to the non-parametric nature of frailty scores and the fact that not all data followed a normal distribution; as demonstrated by the kurtosis and skewness values of the variables seen in Table 5.

The frailty score used was the Rockwood frailty score (Rockwood et al., 2005). This was the scoring system used in the chosen hospital and it was routinely calculated by admitting clinicians when a patient was admitted. A higher score indicated a greater level of frailty and thus vulnerability to illness as described before; the scale can be seen (in the format used in NHS hospitals) in appendix 1. 'Early warning score' is a scoring system used throughout the NHS to highlight which patients may be deteriorating or at risk of deteriorating. It is a score based on a patient's different observations, combing together to give a representation of how deranged their observations and thus physiology is. The higher the EWS score, the more likely it is that the patient may deteriorate (Subbe et al., 2001). How patients are scored can be seen (in the format used in NHS hospitals) in appendix 2.

The study was not powered sufficiently to perform logistic regression analysis to assess the predictive relationship between frailty score and 7- and 30- day mortality. This analysis was however performed to assess if frailty score could be used to predict mortality at 7 and 30 days with this sample size.

In summary, the methodology and analysis allowed this study to examine the effect of frailty on the presentation, progression and mortality of inpatients treated for HAP on two case study medical wards in a DGH, within the UK.

Characteristic	Mean (+/- sd)
Age (years)	81 (12)
Gender	23 Female/ 14 Male
Frailty Score	6.38 (1.48)
Comorbidity	**Frequency (%)**
Chronic obstructive pulmonary disease	15 (40.5)
Cancer	14 (37.8)
Hypertension	12 (32.4)
Other lung Disorder	10 (27.0)
Ischaemic heart disease	10 (27.0)
Atrial fibrillation	8 (21.6)
Osteoarthritis	7 (18.9)
Diverticular disease	4 (10.8)
Congestive cardiac failure	3 (8.11)
Other cardiac condition	3 (8.11)
Type two diabetes mellitus	3 (8.11)
Chronic kidney disease	3 (8.11)
Cerebrovascular accident	2 (5.41)
Other	70
Smoking status	**Frequency (%)**
Current smoker	7 (18.9)
Ex-smoker	10 (27.0)
Non-smoker	15 (40.5)
Not documented	5 (13.5)

Table 4. Baseline characteristics of study population.

Ethics

The study had ethical approval from Bangor University (application number: 2020-16685) and approval from the local NHS health board audit team (application number: 19/364). No novel data was collected that wasn't already recorded as part of each patient's standard care. No patient's care

was affected by the study in any way. All data was stored securely and anonymously as per the university and NHS clearance.

3.4 Results

Summary: frailty score and mortality

Patients who died at 7 and 30 days had higher mean frailty scores than those who were alive at the same times. The predictive power of this relationship could not be assessed in this study.

Summary: frailty score and presentation

Frailty score was not found to be significantly correlated with a change in presenting features at time of diagnosis of HAP.

Population characteristics

The mean age of cases was 81 years and the sample consisted of 23 females and 14 males. The mean frailty score was 6.38. The mean time from admission to diagnosis of HAP was 26.3 days, but this had great variation (standard deviation (sd) +/- 27.2). Further information regarding baseline characteristics can be seen in Table 5. The most common underlying comorbidities were Chronic Obstructive Pulmonary Disease (COPD) (40.5%), cancer (37.8%), hypertension (32.4%), other lung disorders (27.0%) and ischaemic heart disease (27.0%). Mean and median values for the dependant variables (i.e. observations and blood tests) at the time of diagnosis are represented in Table 5. It is these characteristics that were studied through correlational analysis of their relationship to frailty score. Measurements of these characteristics at time of diagnosis for each case were correlated against frailty score at admission. Spearman's rank correlation coefficient was then used to assess for significant correlation. Table 5 also describes the skewness and kurtosis values for the independent and dependant variables.

Characteristic	Mean (+/- sd)	Median	Skewness	Kurtosis
Age	81 (12)			
Frailty Score	6.38 (1.48)	6	-0.594	0.815
Time from admission to diagnosis	26.3 (27.2)	16	2.19	5.38
Early Warning Score	4.92 (3.07)	5	0.0686	-1.02
Respiratory rate	22.9 (6.97)	20	1.52	1.12
Heart rate	93.3 (16.3)	93	-0.118	0.145
Systolic blood pressure	125 (22.0)	124	0.404	-0.716
Temperature	37.3 (1.03)	37.1	-0.621	1.30
Diastolic blood pressure	70.6 (18.1)	70	1.66	5.08
White cell count	14.1 (5.13)	14	-0.0265	-0.560
C- reactive protein (CRP)	113 (86.0)	88	1.68	4.22

Table 5. Characteristics at time of diagnosis.

Frailty score and mortality

Of the 37 patients, 34 were still alive after 7 days from HAP diagnosis, providing a mortality of 8.11% at 7 days. 30 were still alive after 30 days, providing a mortality of 18.9% at 30 days. Analysis of frailty scores and mortality data showed that the mean (+/- sd) frailty score of those who had died at 7 days was 6.80 (2.14) and the mean frailty score of those alive at 7 days was 6.41 (1.31). The mean frailty score of those who died at 30 days was 7.00 (1.76) and the mean frailty score of those alive at 30 days was 6.30 (1.32). Therefore, in this study, those who died at 7 and 30 days may have been more frail than those who were alive at the same times.

The differences in frailty scores were small, however the frailty scores of the included patients were largely very similar and the distribution had a standard deviation of only 1.48 (mean 6.38). Nonetheless, the overlapping standard deviations of the mean frailty scores cast doubt on any relationship.

The small sample size used in this study was intended to answer the pilot study questions with sufficient power to allow correlational analysis. This study was not intended to allow logistic regression analysis and was not sufficiently powered to do so to assess this relationship further.

Binary logistic regression analysis was performed on the data to prove this and also to explore if frailty score could predict mortality in this sample. Analysis showed that in this study frailty score was unable to predict 7 day (p=0.490) and 30 day (p=0.154) mortality from HAP.

Frailty score and presentation

Correlations between frailty score and the characteristics found in Table 5 at time of diagnosis were found to be minimal and not statistically significant at the 5% level. The strongest correlations were between frailty score and time from admission to diagnosis and heart rate (rho= 0.246 and -0.276 respectively) but these were not significant (p=0.142, p=0.098 respectively). The full results for this analysis for each presenting characteristic detailed above are represented in Table 6.

Characteristic	Spearman's rho	p-value
Time from admission to diagnosis	0.246	0.142
Early Warning Score	-0.058	0.732
Respiratory rate	0.053	0.758
Heart rate	-0.276	0.098
Systolic blood pressure	-0.051	0.763
Temperature	-0.163	0.373
Diastolic blood pressure	-0.157	0.353
White cell count	0.205	0.252
C- reactive protein (CRP)	0.057	0.744

Table 6. Spearman's rho and p values for frailty score and characteristics at diagnosis correlations.

3.5 Discussion

Frailty score and mortality risk

Within the sample explored in this study, those patients with HAP who had died at 7 days from diagnosis had a higher mean frailty score than those that were still alive. Similarly, those patients with HAP who had died at 30 days from diagnosis had a higher mean frailty score than those that were still alive; 7.00 compared to 6.30. A higher frailty score within this sample was therefore associated with a higher mortality rate at both 7 and 30 days. This study was not sufficiently powered to perform logistic regression analysis due to the sample size. This research therefore could not conclude that an increasing frailty score was significantly correlated with an increased risk of mortality but it did show an apparent association. Also of note were the overlapping standard deviations of the means at both 7 and 30 days. This study was also insufficiently powered to assess the predictive power of frailty score for mortality that may or may not exist. Larger studies with sufficient power may be able to perform this analysis and assess the significance of any relationship.

To the researcher's knowledge, this relationship had not been studied before and therefore could not be discussed directly in comparison with the literature. However, frailty is a syndrome arising from the effect of a combination of age, comorbidities and performance status (Hoogendijk et al., 2019; Fried et al., 2001; Clegg et al., 2013). The potential association with mortality risk was in agreement with the findings of some authors who studied these factors that contribute to frailty but not others (Sangmuang et al., 2019; Takano et al., 2002; Feng et al., 2019b; Celis et al., 1998; Lee et al., 2005; Gomez et al., 1995). The issue of discrepancy in the literature regarding these risk factors was described in the scoping review (Chapter Two). This began to explain why the literature could both agree and disagree with the findings of this study. This discrepancy in the literature, evidenced further here demonstrated the very reason that frailty was studied in this thesis in the context of HAP.

In order to explain this further, this Chapter must revisit Chapter Two. In Chapter Two it was reported that Sangmuang et al (2019) and Takano et al (2002) found that some comorbidities were risk factors for mortality from HAP but also that some comorbidities were not risk factors. The researcher wondered if this may have been a result of other factors rendering the frailty of these patients to be lower. If frailty was not considered and adjusted for then comorbidities may be found to not be associated, because the overall frailty was the important issue for mortality. It may also be

that some comorbidities affected frailty score (and therefore an effect on HAP mortality risk) more than others. This warrants further research.

Feng et al (2019b) and Celis et al (1988) found that increasing age was associated with increased mortality risk, thus supporting the findings of this paper because age contributes to the frailty syndrome. However, Takano et al (2002), Sangmuang et al (2019), Lee et al (2005) and Gomez et al (1995) all found that age did not increase mortality risk. As with comorbidities, if other uncorrected factors were contributing to the frailty syndrome in these cases then the age may not have been independent.

When age has been found to be associated, it may have been that the resultant frailty (that partly depends on age) in that population happens to be correlated to age. Age may therefore only be found to be associated with mortality risk in populations where it happens to also correlate with frailty score. Thus, it is frailty score that is important, not the age independently by itself. This may therefore go some way to explain the discrepancy in the findings regarding age and comorbidities and explains why the researcher studied frailty.

Performance status or recent general deterioration were not studied in relation to mortality risk by any papers found in the scoping review in Chapter Two so cannot be considered in this discussion.

Overall, the issues raised with regard to frailty score and mortality risk identified in this exploratory pilot study clearly warrant further investigation as a matter of urgency. Furthermore, the interaction between age, comorbidities and performance status to produce the frailty syndrome needs further attention.

Nonetheless, the findings of this thesis suggest that frailty score is associated with an increased risk of 7 and 30 day mortality. Determination of the statistical significance of this relationship is needed. The difference in frailty scores between the groups who were dead and alive at these times were small. The clinical significance of any differences must therefore also be considered. Future studies with greater power may show similar differences that may have statistical significance whilst still remaining clinically insignificant. Further research should also therefore focus on assessing what differences would be clinically significant. This information could guide clinicians when making both treatment and escalation plans. It can also aid in discussions with patients and their families regarding prognosis.

Frailty score and presentation

This study showed that within the population studied, frailty score was not significantly associated with any change in EWS, observations or inflammatory markers at time of diagnosis. Additionally, it was not associated with a change in the time between admission and development of HAP.

These finding are of significance to healthcare professionals and demonstrate that further research with a greater sample size is warranted. This study's findings suggest that people with a high frailty score respond in the same way as those with lower scores when they develop HAP. This information can aid healthcare professionals in diagnosing and treating all patients. If it is known that physiological presentations following HAP acquisition (observations, blood tests, warning scores) are not being affected by their level of frailty then it is easier to assess how unwell patients are. This is because the physiological changes can be assumed to be secondary to the pneumonia without any confounding influence from the frailty syndrome. These patients, however frail, can be thought of just like their peers who may be less frail. Treatment and escalation decisions can then be provided at the appropriate level and urgency without confusion.

The finding that suggested that frailty score does not seem to be related to the time it takes to develop HAP from admission is also useful. Clinicians may be able to use this information to aid in their monitoring of patients for HAP and attempts to prevent HAPs occurring, as appropriate and feasible. Clinicians attending any patient who has become acutely unwell may find it useful to know that frailty score does not seem to affect the likelihood of HAP being responsible for any deterioration at any time during an admission. This information can therefore further aid appropriate treatment and escalation decisions.

In summary, the findings of this preliminary study, should they be supported by further research, are of great importance and value to clinicians. Improved knowledge of the importance of frailty for mortality rates alongside its lack of impact on presentation may help guide a wide range of clinical decisions.

3.6 Modelling: moving beyond the scoping review

The findings of this preliminary empirical research add valuable information to the evidence base surrounding HAP. The positive and negative findings are both of equal utility to healthcare professionals as explained above. Knowledge that frailty score does not affect how patients with HAP present, but that it may affect how likely it is that they will die from a HAP can guide decision making and escalation plans.

The empirical work in this chapter furthered the synthesis of a model for how patients are put at increased risk of mortality from HAP. In the scoping review in Chapter Two of this thesis a model was produced demonstrating how different risk factors increase the risk of acquisition of HAP. This required knowledge about which factors were associated with HAP acquisition as well as those that weren't. In this chapter, the novel exploratory pilot study provided further understanding to which factors may be associated with an increased risk of mortality from HAP by identifying one potential factor.

This work therefore added to the development of a model for mortality risk from HAP. A proposed early model for this can be seen in Figure 5, describing how patients may be put at risk of mortality from HAP. The factors of age, comorbidities, performance status and general deterioration have either contradictory evidence for their impact on mortality risk, or there is no data. If these issues together contribute to the frailty syndrome (Clegg et al., 2013; Fried et al., 2001; Hoogendijk et al., 2019; Mitnitski et al., 2001), then frailty may be a better assessment of risk. The work in this chapter has identified a possible correlation between frailty score and mortality risk from HAP. Very recent work by other researchers has discovered clear evidence of frailty's association with mortality in other situations (Church, et al., 2020). This would support the findings of this research that frailty score was associated with mortality risk from HAP.

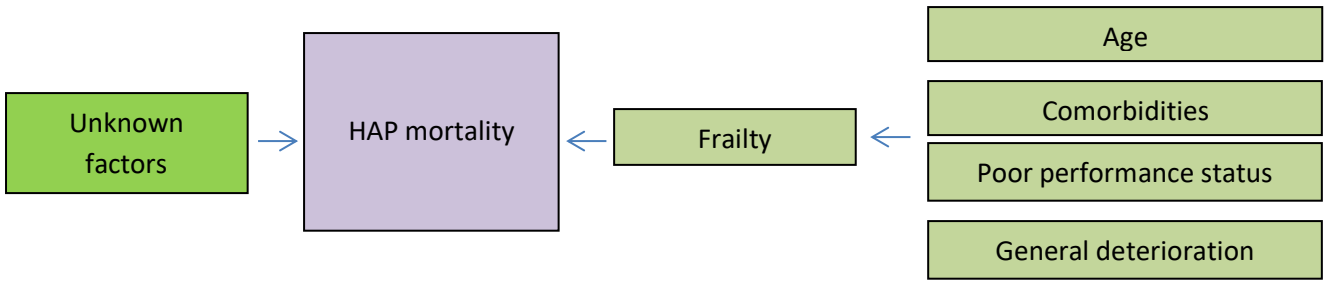


Figure 5. Early modelling of how patients are put at risk of mortality from HAP.

If frailty score is found to not be associated with an increased risk of HAP mortality after further investigation of significance then it may be the case that it is an individual component of frailty (i.e. age, performance status, comorbidities) that is associated with mortality risk. Of course it is also possible that none of these factors are associated, or that they are only significant in particular combinations or circumstances. Discovering that frailty score, or the possible contributing factors are not associated with mortality risk would be equally helpful in the production of future models for mortality risk. The paucity of research into these risk factors and others with regard to mortality risk identified in Chapter Two demonstrated the importance of further research to improve understanding of these relationships. The study within this chapter has begun this work.

3.7 Conclusion

The aim of Chapter Three was to begin the work called for in Chapter Two; it aimed to investigate understudied risk factors for mortality from HAP. The particular focus of study was the previously unstudied issue of frailty in the context of HAP. More specifically, it aimed to assess the relationship between frailty score and both the presentation of HAP and mortality risk.

The researcher hypothesised that an increasing frailty score would be associated with:

1. An increased risk of mortality from HAP
2. A lower early warning score
3. A smaller rise in inflammatory markers

In this sample the patients who had died at 7 and 30 days from diagnosis had a higher mean frailty score than those who were still alive. This is an interesting association that warrants urgent further research to assess the significance and predictive power.

Information regarding frailty score as a risk factor for mortality from HAP adds to the ability to produce a model for HAP mortality risk similar to that produced in part two for HAP acquisition risk. The findings of this study suggest that increased frailty score is associated with increased mortality risk and an early model has been produced. Further research into the significance and predictive power will inform future modelling.

Hypotheses 2 and 3 were disproved and the findings of this study supported the null hypothesis for each. These findings were equally as valuable to clinicians and healthcare professionals compared to if the null hypothesis had been rejected. Knowledge that frailty score did not affect how patients with HAP present can guide decision making and escalation plans.

The findings of this work within Chapter Three may therefore aid healthcare professionals in caring for frail patients and patients with HAP. Additionally, the findings add clarity to the collective knowledge regarding risk factors for mortality from HAP. This chapter therefore begins to answer the call from Chapter Two for urgent novel pilot studies to increase understanding and provide clarity to the literature. This new information begins the work to produce a model describing how patients are put at risk of mortality from HAP.

Chapter Four

Hospital Acquired Pneumonia and Frailty: the relationship

4.0 Introduction

Chapters Two and Three identified important novel findings regarding both hospital acquired pneumonia and frailty. The findings of Chapter Two regarding risk factors for HAP acquisition and mortality, and the literature surrounding HAP in general informed Chapter Three. Contradictory information regarding age and comorbidities, and a paucity of research into performance status and general deterioration led to the call for further research into risk factors for mortality risk from HAP.

The pilot study conducted within Chapter Three was a study of the importance of frailty within the context of HAP. It assessed the relationships between frailty and HAP presentation and mortality.

Chapter Four summarises and frames the findings in the wider context of nosocomial infections and provides recommendations for further work.

4.1 Contribution

The focus of study in this thesis was hospital acquired pneumonia (HAP). This disease is one variety of nosocomial pneumonia and is thus one variety of nosocomial infection (Nair & Neiderman, 2013). The study of HAP was therefore important as it may potentially add to the collective global effort of reducing the immense burden of nosocomial infections (WHO, 2011). HAP was chosen as the nosocomial infection of interest for this thesis after a preliminary literature search revealed that it is poorly studied outside of intensive care units (Sopena et al., 2014; Burton et al., 2016). This thesis contributed towards further improving understanding of HAP as part of attempts at reducing the burden of this important nosocomial infection.

Frailty, deemed a highly problematic consequence of an aging population (Clegg et al., 2013) was identified in Chapter Two as an emergent theme of importance with regard to HAP but one that had not been studied before (to the researcher's knowledge). This lack of research into frailty in the context of HAP, alongside a lack of research into HAP mortality risks stimulated the researcher to propose studying these issues further. Chapter Three contains a novel pilot study investigating the relationship between frailty and HAP presentation, progression and mortality.

The Rockwood frailty scale (Rockwood et al., 2005) was utilised to stratify frailty scores of patients in a district general hospital. This frailty scale provides a measure by which an individual's frailty level can be attributed a value and allows easy comparison of the frailty 'level' of different patients.

The study in Chapter Three therefore explored the relationship between frailty score, as per the Rockwood scale and HAP. More specifically, it studied the effect frailty score had on how HAP presented in patients and how it affected mortality risk. This study was novel in both design and interest and therefore the researcher hoped would add valuable insight into a hitherto poorly researched area. Increasing research into the field of HAP, nosocomial pneumonia and nosocomial infection may help improve patient care across the world given the impact that these diseases have (WHO, 2011). Calls for healthcare systems to be adapted based on discoveries regarding frailty had been made previously in the literature (Cesari et al., 2017). This thesis adds to the literature surrounding both frailty and nosocomial infections and may assist in the design of future healthcare systems, or adaptation of existing ones.

4.2 Discussion: reflections on the findings

Revisiting the scoping review

In Chapter Two of this thesis the researcher described the insights gained from a scoping review of the available literature on HAP. More specifically this review was a study of the evidence surrounding risk factors for acquisition and mortality from HAP. Through thematic analysis and synthesis of the findings this scoping review provided novel insight into the understanding of these risk factors. The literature could be summarised and models describing the evidence base could be synthesised.

The conclusions of Chapter Two were as follows:

1) The risk factors for acquisition of HAP can be placed into two meta-themes
    a. Any factor that increases the risk of a breakdown of the protective mechanisms that stop aspiration of oral flora
    b. Any factor that increases the risk of a loss of performance status or mobility
2) Of these two meta-themes, (b) may be a proxy for (a) in that it represents an individual at higher risk of the themes in (a)
3) A third meta-theme emerged from the evidence describing fracturing of the literature

The third meta-theme described the fact that the literature surrounding risk factors for HAP acquisition and mortality was full of contradictory findings and conclusions, and there was a significant variation in the frequency with which different risk factors were researched. Furthermore, there was very little evidence regarding risk factors for mortality from HAP (Takano et al., 2002; Sangmuang et al., 2019; Lee et al., 2005, Gomez et al., 1995; Feng et al., 2019b; Celis et al., 1988).

The findings from Chapter Two allowed the production of two models. The first model demonstrated how risk factors seemed to lead to an increased risk of HAP acquisition (Figure 2). The second model demonstrated how the literature surrounding HAP has become fractured (Figure 3). A model for risk factors for HAP mortality could not be produced due to the paucity and discrepancy in the fractured literature (Sangmuang et al., 2019; Takano et al., 2002; Feng et al., 2019b; Celis et al., 1998; Lee et al., 2005; Gomez et al., 1995).

The two meta-themes of ‘any factor that increases the risk of a breakdown of the protective mechanisms that stop aspiration of oral flora’ and ‘any factor that increases the risk of a loss of performance status or mobility’ provided possible areas for intervention. Improving understanding of how risk factors for HAP acquisition interact and form themes and meta-themes provided insight into how healthcare providers could reduce the risk of HAP acquisition.

The value of such insight realised through research such as in Chapter Two showed why the fracturing of the literature also identified in Chapter Two must be mitigated. If clarity is improved, then healthcare providers may find it easier to adapt systems and improve care as called for (Cesari et al., 2017). If paucity of research is minimised then this may further improve the fracturing and enable the production of further models to describe additional risks; one such example being mortality risk.

This analysis and synthesis of the literature via means of the scoping review therefore demonstrated the urgent need for novel pilot studies into risk factors for mortality from HAP. The scoping review

also informed which risk factors were of paramount importance to investigate as a result of the fractured literature. The conclusion of Chapter Two suggested that further information regarding risk factors for mortality may allow the production of a model for how risk factors increase the risk of HAP mortality.

Revisiting the pilot study

In Chapter Three of this thesis the researcher sought to answer the call for novel pilot studies into risk factors for HAP mortality emerging from the scoping review of the evidence. The chapter described a piece of empirical research conducted at a district general hospital in North Wales, UK. The most important novel issue proposed and explored in Chapter Three (based on findings in Chapter Two) was frailty- a clinical condition that results from a decline in physiological reserve with age (Clegg et al., 2013). Frailty had previously been shown to place people at a higher risk of numerous negative outcomes, for example nursing home placement, hospitalisation, falls and death (Kojima G, 2016; Kojima G, 2015; Fried et al., 2001; Clegg et al., 2013).

It was identified in Chapter Two that there was a paucity of evidence surrounding performance status or general deterioration and mortality from HAP (see Table 3). There was also discrepancy in the evidence surrounding age and comorbidities and mortality from HAP (Feng et al., 2019b; Celis et al., 1998; Takano et al., 2002; Sangmuang et al., 2019; Lee et al., 2005; Gomez et al., 1995; Stenlund et al., 2017; Alsuraikh et al., 2008; Rothan-Tondeur et al., 2003; Hanson et al., 1992) These factors all form part of the frailty syndrome and contribute to a patient's frailty score (Rockwood et al., 2005). Frailty score was chosen by the researcher as a measure of performance status and general deterioration because of the close relationship with these risk factor themes and its association with many adverse outcomes (Fried et al., 2001; Clegg et al., 2013). It was also a measurement in common use in the hospital where the research took place.

Previous papers examined elements of performance status, specifically eating dependency (Harkness et al., 1990), poor functional status (Mazière et al., 2013) and immobility (Stenlund et al., 2017) and their relationship to HAP acquisition. All three papers found that these elements were associated with an increased risk of HAP acquisition.

Scoring systems for frailty exist to describe the syndrome and the study in Chapter Three utilised the system devised by Rockwood et al (2005) to stratify the patients included in the study by level of frailty. It was this system that was in use in the hospital where the empirical research took place. The

system allowed correlations between frailty score and various markers of HAP severity and progression, as well as mortality data to be made.

It has been proposed that as the population ages it follows that it will become more frail (Hoogendijk et al., 2019). Frailty may therefore become an increasingly important issue in healthcare settings (Clegg et al., 2013). The importance of clinicians, healthcare workers and scientists knowing the impact of this factor on important diseases such as nosocomial infections is therefore clear. The cost of nosocomial infections in both the NHS (Guest et al., 2020) and worldwide (WHO, 2011) mean that all efforts to reduce incidence and mortality are of value. The research described in Chapter Three was therefore comprised of an exploratory pilot study into the relationship between frailty score and HAP presentation and mortality risk, as described above. This pilot study of frailty within the context of HAP produced the following preliminary conclusions:

1) In this sample, the patients who had died at 7 and 30 days from diagnosis had higher mean frailty scores than those who were still alive
2) In this sample, frailty score was not associated with significant differences in how patients presented with HAP

The first conclusion of Chapter Three is of interest in how it can inform patient care. If a patient is found to have a higher frailty score, it may mean that they are more likely to die should they acquire a HAP. It may be possible for healthcare systems to instigate additional measures to mitigate the risk of acquisition of HAP in frail patients, who may be more likely to die than their less frail peers. The model in Figure 2 in Chapter Two could help guide possible areas for such interventions.

Future studies with sufficient power to study the significance and predictive power of this association are urgently needed to explore these preliminary findings further and provide clarity on this relationship. If the association is not significant and logistic regression analysis deems it not to be predictive then healthcare systems would know that frailty score did not bear an implication for mortality risk. This would add clarity to the fractured literature described in Chapter Two and aid the design of healthcare systems to take frailty into account as called for by Cesari et al. (2017).

The negative findings of this exploratory pilot study regarding HAP presentation and frailty are also of great importance. If supported by further research, these preliminary findings can aid clinicians and healthcare professionals in caring for frail patients by demonstrating that they can expect all patients, regardless of frailty score, to present in the same way with HAP. This is because frailty score does not seem to be correlated with any of the measured presenting features of HAP. By guiding further research, which may support these preliminary findings, this knowledge may help

guide how patients are cared for. Additionally, clarity to the collective knowledge regarding risk factors for mortality from HAP may be gained, therefore helping to mitigate the fracturing of the literature found in Chapter Two.

In summary, Chapter Three began to answer the call from Chapter Two for urgent novel pilot studies into risk factors for mortality from HAP. The preliminary findings demonstrated a need for new research to provide an increased understanding of HAP, the role of frailty in this context and provide clarity to the literature.

Although the results from Chapter Two were unable to produce a model describing the risk factors for HAP mortality, the findings in Chapter Three advanced this process by providing information regarding one risk factor, namely frailty. An early version of this model can be seen in Figure 5. Chapter Three also confirmed the need for further larger studies to build on this exploratory pilot study. Indeed, further larger studies into the issue of frailty and HAP mortality, as well as further pilot studies into other potential risk factors for mortality from HAP are needed urgently. The relationship between frailty score and HAP mortality risk needs urgent clarification regarding its significance and predictive power. The pilot study in Chapter Three has only studied one risk factor for HAP mortality. The scoping review in Chapter Two identified many possible others, but the fracturing of the literature currently prevents any modelling. Nosocomial diseases impart enormous burden on societies across the globe (WHO, 2011) and it is of vital importance that everything is done to mitigate them.

4.3 Synthesis and modelling HAP and frailty

Through pre-existing literature, and the experiences of the researcher as a practising clinician, the impact of nosocomial infections globally and within the NHS was well known about (WHO 2011). Hospital Acquired Pneumonia, as one form of nosocomial infection therefore demanded attention (Nair & Neiderman, 2013). Scanty evidence surrounding HAP led to the work undertaken in Chapter Two of this thesis.

The findings of Chapter Two were of a fractured and contradictory literature surrounding the issue of HAP. In and amongst this the researcher was able to bring out themes of risk factors for HAP acquisition. This allowed the production of models to describe how individuals are put at risk of acquiring HAP (Figure 2). The fracturing of the literature was also modelled in Chapter Two (Figure

3); it was this fracturing that prevented the production of a similar model for mortality risk. Risk factor themes identified in Chapter Two stimulated the researcher to investigate the involvement of frailty in the HAP environment.

Frailty was something known to be of importance, and closely related to some of the themes identified in the scoping review (Fried et al., 2001; Clegg et al., 2013). The lack of research into mortality risk identified in Chapter Two led to the researcher investigating the involvement of frailty in this aspect of HAP, alongside HAP presentation. Chapter Two therefore guided and informed the work in Chapter Three where the researcher conducted a novel pilot study into the relationship between frailty and HAP presentation and mortality risk.

The novel pilot study described in Chapter Three investigated the issue of frailty within the context of HAP. The study identified that frailty score may be associated with an increased risk of mortality, but this required further investigation with higher powered studies. The study also discovered that frailty score is not significantly correlated with any of the measured presenting features of HAP or markers of severity. As previously described, this may help improve the care of patients with HAP.

The scoring system for frailty utilised in Chapter Three was that devised by Rockwood et al (2005). Due to a complex and multifactorial aetiology several definitions for frailty exist and there are a variety of systems of stratifying it (Rohrmann, 2020). The 'frailty phenotype' was devised as one such method which categorises patients as frail based on the presence of specific physical characteristics (Fried et al., 2001). Alternatively, the 'frailty index' views frailty as an accumulation of health problems and categorises patients based on how many of these problems they have. These problems are not just physical characteristics as in frailty phenotype, but also include disabilities and social issues (Mitnitski et al., 2001). Concerns about the validity or utility of these systems led Rockwood et al to devise a system that utilised clinical judgment to interpret all of this information (Rockwood et al., 2005). It was the Rockwood clinical frailty scale that was the system in place in the hospital in which the pilot study took place and therefore was the system utilised in Chapter Three.

Frailty has to be considered in context as it has both a variable prevalence and variable significance within populations (Rohrmann, 2020). Comparing the effect of frailty within different populations must therefore take this into account. The use of clinical frailty scales that rely on clinical judgment aims to standardise assessment of frailty. However, different systems exist and therefore practice is not standardised across the globe (Morley et al., 2013). Using different tools or frameworks to study frailty, alongside variable context and definitions may make different populations or outcomes difficult to compare. These issues render research into frailty and use of the systems in clinical

practice complex and time consuming. The work done in this thesis regarding frailty has been conducted within the context of HAPs in a district general hospital. Frailty is known to be closely related to many patient characteristics (Fried et al., 2001; Clegg et al., 2013). The close relationship between comorbidities and various other patient characteristics mean that the evidence collected is relevant to these issues but may have limited value otherwise.

The issues of variable definitions, methods for measuring and close relationship with any potential outcomes render the concept of frailty difficult to study. Figure 6 is a diagram illustrating the issues surrounding studying frailty. It highlights why it is a complex concept and studying it (in this case in the context of HAPs) is a difficult undertaking and acts as a heuristic model for the issue.

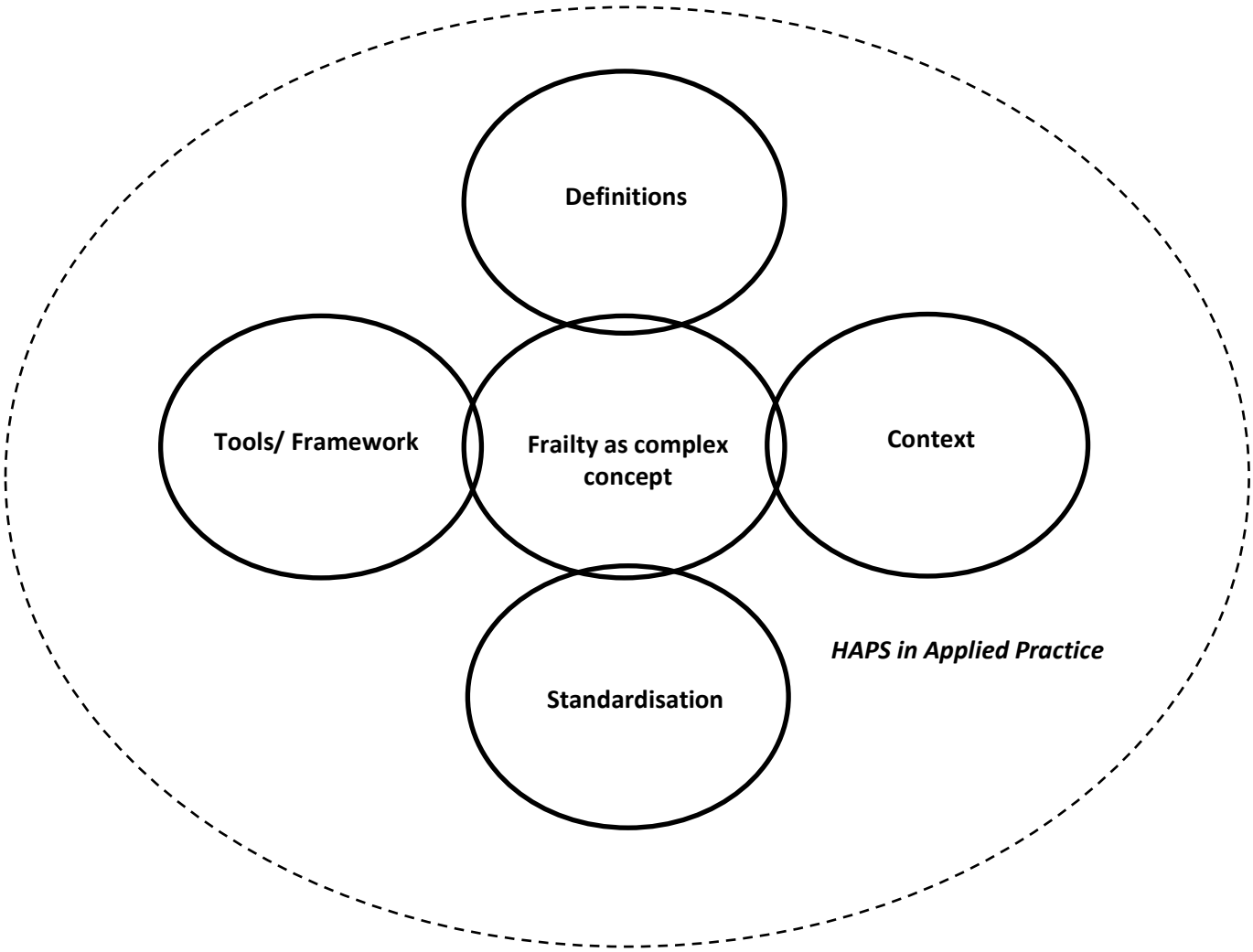


Figure 6. Frailty as complex concept: a heuristic model.

Within the context of HAP, frailty's involvement with presentation and mortality risk had not, to the researcher's knowledge, been studied before this thesis. Chapter Three contains interesting novel insights into the issue of frailty within the context of HAP. The researcher hopes that this new information can add to the collective knowledge regarding both frailty and HAP. The conclusions may assist healthcare providers and healthcare systems to adapt to frailty, consider the impact on HAP and therefore improve the care that can be provided to affected patients or those at risk. Issues contributing to frailty may be amenable to intervention (Morley et al, 2013; Carneiro et al., 2017; Kojema G, 2016); therefore, reducing frailty may reduce HAP mortality if the two are associated.

The issue of HAP forms one element of the wider problem of nosocomial pneumonias and nosocomial infections (Nair & Neiderman, 2013). Through innovative design and rigorous methodology, this thesis provided novel insights into nosocomial infections.

4.4 Reflections on approach and methods

This thesis utilised two different powerful research methodologies in order to improve understanding of HAPs. Chapter Two contains a scoping review that was performed to study the risk factors for acquisition and mortality from HAP. Chapter Three contains a novel pilot study aimed at improving understanding of frailty within the context of HAP; more specifically, the relationship between frailty score and HAP presentation characteristics and HAP mortality rates. The pilot study utilised a case-study approach to perform documentary analysis of a series of HAP cases within a case series of a season of HAPs.

The scoping review utilised strict methodology that is widely accepted as appropriate for this context (Levac et al., 2010; Miles & Huberman, 1994). Limitations of this methodology included its inclusion of lower quality evidence. This is an inevitable outcome from the desire to include a wide range of evidence which is central to the aim of any scoping review (Levac et al., 2010). Analysis of the use of the scoping review format is included within Chapter Two in much greater detail.

The researcher believes that the outcomes of the research conducted in Chapter Two could not have been achieved without the use of a scoping review. Without the broad, open approach to literature review many aspects of the findings of this thesis would have been missed. This methodology allowed the researcher to gain valuable novel insights into the risk factors for HAP acquisition and

mortality and the state of the current literature. It also informed the work that underpinned Chapter Three.

On a personal level, the researcher, being new to postgraduate research and elements of qualitative research found the approach useful to help build up new skills surrounding literature reviewing, thematic analysis, synthesising evidence and producing models.

The empirical work conducted in Chapter Three allowed the researcher to study frailty in the context of HAPs. It allowed investigation into the relationship between frailty score and HAP presentation and mortality risk. The methodology is described in detail in Chapter Three. The case-study methodology utilised in Chapter Three has previously been shown to be an appropriate and powerful methodology in research into healthcare (Lalor et al., 2013).

Strengths of the study included the rigorous data sampling from two wards conducted by the researcher and another researcher who was collecting the same data for a different project. Suitability of all participants for inclusion in the study was agreed upon by both of these researchers. Additionally, all data collected by one researcher for the study was double checked by the other co-researcher to confirm accurate recording of the data. All data collected was objective and remains recorded in the file of every participant as part of their ongoing hospital care. As the study was entirely observational and was not contemporaneous the risk of observer bias is very low and there is no risk of recall bias. The fact that the initial documentation of data was performed by practising healthcare professionals who were totally independent to the study is a further important strength.

Limitations of this study included the small sample size. The sample size used in this study was determined to provide the study with sufficient power to answer the research questions in this context. It was also feasible within the time and resources available for an exploratory pilot study. Further limitations included the fact that 100% of participants happened to be of white British ethnicity. This limits any conclusions that can be drawn to potentially only being applicable to this group. This is a challenge faced by all international research unless performed over multiple centres in multiple countries including multiple ethnicities as participants.

The analysis in this study did not involve adjusting for any other variables when assessing relationships between frailty score and the dependant variables. This was a deliberate decision made by the researcher. The scoping review in part two of this thesis demonstrated that there is highly contradictory information regarding risk factors for acquisition and mortality from HAP. It was therefore decided that to adjust for confounders would be impossible (as it was very unclear what should be adjusted for). Additionally, it would be more representative of the ‘real life’ issues

surrounding this disease which is so poorly understood. It was decided that adjusting incorrectly for confounders that are irrelevant would be more damaging and render the results of this study less useful than to not adjust.

Although initial documentation of data was performed by independent practising healthcare professionals, a further minor limitation is that the data extraction was performed by the two researchers. These individuals are not independent to the study and there is always a risk of bias from this. This research was performed as part of two individuals' separate assessed Masters of Research qualifications and the researchers were inexperienced. However, they were supervised and advised by experienced researchers. Furthermore, being practising medical practitioners they were bound by strict professional codes of practice.

One additional limitation was fairly novel and this was the outbreak of the coronavirus pandemic. The first case of coronavirus seen in the study hospital was in mid-March 2020 and no cases were identified on the two wards used in this study until over two weeks later. Data collection for this study was stopped in early March in order to minimise the risk of covid-19 becoming a confounding factor. No patient included in this study tested positive for covid-19 or was symptomatic for the disease. However, the researcher could never be certain that all participants were free from the virus as none were tested for it (being inpatients before the outbreak). Whilst highly unlikely, covid-19 may therefore have been a confounding factor in this study and it is important to mention the issue in this discussion.

The outbreak of the coronavirus pandemic required the cessation of data collection. On a personal level this was frustrating to the researcher as further data could have been collected should this not have occurred. Thankfully enough cases of HAP had been collected to sufficiently power the study as per original calculations at the time of study design.

Within the literature, Mazière et al (2013) called for further prospective research to examine the power of the relationship between disability and nosocomial infections. Like performance status, disability forms a part of the frailty syndrome (Rockwood et al., 2005) and therefore the study in this thesis goes some way to begin answering this call for more research.

All of the above strengths of the work conducted in both Chapter Two and Chapter Three result in important novel work in this field. The findings of this thesis, alongside reflection upon the methodologies used allow the following recommendations to be made.

4.5 Recommendations

Policy

- HAPs are important nosocomial infections that need to be mitigated against across the globe
- Thus far, research into HAP has led to contradictory evidence, this demands urgent attention and funding for researchers to improve clarity
- Risk factors for HAP acquisition have been identified where interventions could help reduce rates
- Frailty, evermore realised as an important issue within healthcare demands urgent further attention in the impact it has on HAPs and other nosocomial infections
- Healthcare systems should be modified as research provides evidence to mitigate against both frailty and HAP

Research

- Urgent research into all issues surrounding HAP is urgently needed
- Research should build on the methodology and findings of this single-centre exploratory pilot study with further novel pilot studies into risk factors for mortality from HAP
- These pilot studies should focus on studying areas where the literature contains contradictory evidence or a paucity of evidence
- Further, larger studies into frailty score and HAP mortality are urgently needed
- Studies across multiple sites may be of utility to render findings more applicable to wider populations
- Further research may aid the synthesis of models that identify areas where intervention could reduce negative outcomes from HAP
- Generally, modelling risk factors could help reduce negative outcomes from nosocomial infections

Practice

- Healthcare professionals should keep up to date with evolving research surrounding HAPs
- Risk factors for HAP acquisition form two meta-themes, intervening in these issues could help reduce rates
- Evidence for mortality risk from HAP is lacking
- Frailty may play an important part in mortality risk from HAP, further research may provide clarity
- Frailty may not affect how HAPs present clinically

4.6 Conclusion

This thesis identified several novel issues surrounding the issue of hospital acquired pneumonia. The scoping review of the available literature in Chapter Two identified that risk factors for acquisition of HAP form two meta-themes:

a. Any factor that increases the risk of a breakdown of the protective mechanisms that stop aspiration of oral flora
b. Any factor that increases the risk of a loss of performance status or mobility

Intervention into the issues that make up these meta-themes may reduce rates of HAP.

The scoping review also identified that the literature surrounding HAP is fractured and demands urgent attention to improve clarity. Particular areas of contradictory evidence or a paucity of evidence centred around the concept of frailty.

The novel pilot study in Chapter Three studying frailty in the context of HAP identified that frailty was not significantly associated with an effect on any presenting features of HAP. The study also identified that the individuals with HAP who had died at both 7 and 30 days had a higher mean frailty score than those who were still alive. Frailty may therefore render an individual more likely to die should they acquire a HAP. These findings are preliminary and urgent further research is needed to assess the significance of this finding and any predictive power.

This thesis contains two pieces of novel research utilising different methodologies that both allowed the researcher to produce novel findings that add to the literature surrounding frailty and HAP. All of the work undertaken within this thesis was therefore of significance to the global effort in tackling nosocomial infections. Further research into both frailty and HAP in the context of the wider healthcare environment will add clarity and additional insight into the findings within this thesis. This preliminary work may inform this future research and provide guidance to the important next steps.

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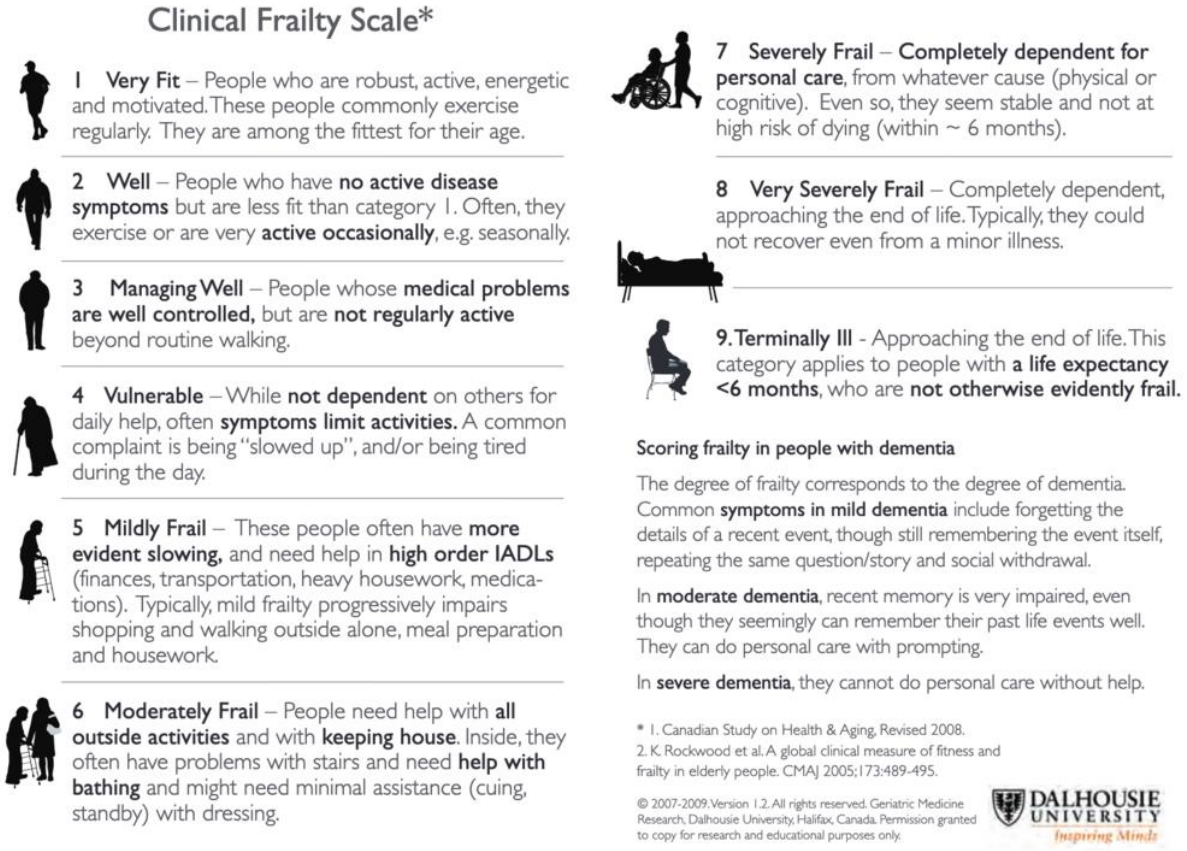
Appendices

Appendix 1



Adapted from: Canadian Study on Health and Ageing, 2008; Rockwood et al, 2005.

Appendix 2

	Physiological Parameters	3	2	1	0	1	2	3
A B	Respiratory rate (bpm)	≤8		9-11	12-20		21-24	≥25
	O2 Saturations (%)	≤91	92-93	94-95	≥96			
	Any supplemental Oxygen		Yes		None			
C	Systolic BP (mmHg)	≤90	91-100	101-110	111-219			≥220
	Pulse (bpm)	≤40		41-50	51-90	91-110	111-130	≥131
D	AVPU score				Alert			VPU
E	Temperature (°C)	≤35.0		35.1-36.0	36.1-38.0	38.1-39.0	≥39.1	

Concern about a patient should lead to escalation, regardless of the score.

Adapted from: 1000 lives campaign; Subbe et al, 2001.