Universidade de Aveiro Escola Superior de Saúde
2019

JOANA MAFALDA LOPES GROSSO DOS SANTOS

Intervenções para prevenir a pneumonia de aspiração em pessoas idosas: Uma revisão sistemática atualizada

Interventions to prevent aspiration pneumonia in older adults: An updated systematic review

Universidade de Aveiro Escola Superior de Saúde
2019

JOANA MAFALDA LOPES GROSSO DOS SANTOS

Intervenções para prevenir a pneumonia de aspiração em pessoas idosas: Uma revisão sistemática atualizada

Interventions to prevent aspiration pneumonia in older adults: An updated systematic review

Dissertação apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Mestre em Terapia da Fala, realizada sob a orientação científica da Doutora Maria da Assunção Coelho de Matos, Professora Adjunta da Escola Superior de Saúde da Universidade de Aveiro e coorientação científica do Doutor Óscar Ribeiro, Professor Auxiliar do Departamento de Educação e Psicologia da Universidade de Aveiro.

Dedico este trabalho aos meus avós, pais e irmão.

o júri

presidente	Prof. Doutor Rui Jorge Dias Costa professor coordenador sem agregação e diretor da Escola Superior de Saúde da Universidade de Aveiro
arguente	Prof. Doutor Tiago Manuel Pombo Alfaro professor auxiliar convidado de Pneumologia da Faculdade de Medicina da Universidade de Coimbra
orientadora	Prof.ª Doutora Maria da Assunção Coelho de Matos professora adjunta da Escola Superior de Saúde da Universidade de Aveiro

agradecimentos

A realização deste trabalho não teria sido possível sem a colaboração e o apoio de algumas pessoas, às quais agradeço profundamente.

À minha orientadora, Doutora Maria da Assunção Coelho de Matos, pela orientação e encorajamento constantes, pela confiança e consideração e pela amizade e compreensão que teve ao longo de todo este processo.

Aos Doutores Óscar Ribeiro e Luís Jesus, pelos seus contributos enriquecedores e sempre céleres.

À minha mãe e ao meu irmão, pelo apoio nesta etapa e sempre.

Muito obrigada!

palavras-chave Pneumonia de aspiração, prevenção e controlo, idosos, disfagia, revisão sistemática

resumo

Introdução: A Pneumonia de Aspiração é uma infeção respiratória aguda que decorre da entrada de fluídos e/ou alimentos com bactérias patogénicas para os pulmões. A sua prevalência aumenta com o envelhecimento e está correlacionada com doenças neurológicas, refluxo gastroesofágico e Doença Pulmonar Obstrutiva Crónica. Tem sido associada a elevadas taxas de reinternamento hospitalar, aumento da duração do internamento e da morbilidade e mortalidade, à diminuição da qualidade de vida e ao aumento dos custos de saúde. Alguns dos seus fatores de risco são modificáveis, por isso, torna-se essencial avaliar o efeito de intervenções preventivas para fundamentar a prática clínica.

Objetivos: Rever estudos clínicos randomizados com foco no estudo de intervenções para prevenir a pneumonia de aspiração em pessoas idosas.

Metodologia: Foi realizada uma revisão sistemática da literatura com base no protocolo registado no PROSPERO. Foram incluídos estudos clínicos randomizados de intervenções para reduzir a incidência de pneumonia de aspiração em indivíduos com mais de 65 anos, publicados entre janeiro de 2002 e julho de 2019 e escritos em inglês. Estudos sobre pneumonia pós-cirúrgica foram excluídos. A qualidade metodológica dos estudos foi avaliada de forma independente por dois revisores utilizando a *Cochrane Collaboration's tool for assessing risk of bias*.

Resultados: Dos 629 artigos identificados, treze foram incluídos na revisão. Seis estudos analisaram intervenções farmacológicas, três artigos abordaram adaptações da dieta e estratégias compensatórias, um estudo avaliou uma técnica de higiene oral, dois estudaram intervenções multidisciplinares e um focou-se numa técnica de reabilitação. Dos estudos incluídos, cinco apresentaram efeito positivo na redução da incidência de pneumonia. A qualidade metodológica da generalidade dos estudos foi avaliada com risco de viés elevado ou indefinido.

Conclusões: Os estudos mais recentes sobre intervenções para prevenir a pneumonia de aspiração em idosos revelaram qualidade metodológica pobre, dificultando a definição de orientações para a prática clínica. Dado o impacto negativo da pneumonia de aspiração nos doentes e nos sistemas de saúde, o desenvolvimento de estudos clínicos mais rigorosos é essencial.

keywords Aspiration pneumonia, prevention and control, older people, dysphagia, sistematic reviews

abstract

Introduction: Aspiration Pneumonia is an acute respiratory infection that results from the entry of fluids (liquids, saliva, secretions) and/or food with pathogenic bacteria into the lungs. Its prevalence increases with aging and it is correlated with neurological diseases, gastroesophageal reflux and Chronic Obstructive Pulmonary Disease. Consequently, it has been significantly associated with high rates of hospital readmission, increased length of stay, morbidity and mortality, and with decreased quality of life and increased health costs. Some of its risk factors are modifiable, so it is essential to evaluate the effect of preventive interventions to support clinical practice.

Objectives: To review randomised controlled trials focusing on the study of interventions to prevent aspiration pneumonia in older adults.

Methodology: A systematic literature review was performed using the protocol registered in PROSPERO. Randomised controlled trials of interventions to reduce the incidence of aspiration pneumonia in individuals older than 65 years, published between January 2002 and July 2019 and written in English, were included. Studies on postoperative pneumonia were excluded. Two reviewers using the Cochrane Collaboration's tool for assessing risk of bias independently assessed the methodological quality of the studies.

Results: Of the 629 articles identified, thirteen met the eligibility criteria and were included in the review. Six studies analysed pharmacological interventions, three articles addressed dietary interventions and compensatory strategies, one study evaluated an oral hygiene technique, two studied the effect of multidisciplinary interventions and one focused on a rehabilitation technique. Of the included studies, five had a positive and statistically significant effect. The methodological quality of most studies was assessed at high or unclear overall risk of bias.

Conclusions: The most recent studies on interventions to prevent aspiration pneumonia in the elderly revealed poor methodological quality, making it difficult to define evidence-based strategies for clinical practice. Given the burden of aspiration pneumonia on patients and healthcare systems, the development of more rigorous clinical trials is warranted.

abreviations

ASP – Aspiration pneumonia
PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO - International Prospective Register of Systematic Reviews
COPD – Chronic Obstructive Pulmonary Disease
RCT – Randomized controlled trial
CRCT – Cluster-randomized controlled trial
OD – Oropharyngeal dysphagia
ASU – Acute stroke unit
EN – Enteral feeding
NGT – Nasogastric tube
PEG – Percutaneous endoscopic gastrostomy
ACE – Angiotensin enzyme converting
BHT - Chinese herbal medicine Banxia Houpu Tang
SDD - Selective decontamination of the digestive tract
QASC - Quality in Acute Stroke Care program
UK – United Kingdom
USA – United States of America
NR – Not reported
N/A – Not applicable
SD – Standard deviation
CT – Computed tomography
CDT - Clostridium difficile toxin
MRSA - Methicillin-resistant Staphylococcus aureus
OR – Odds ratio
HR – Hazard ratio
CI – Confidence interval

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ANNEXES

1. INTRODUCTION

Aspiration is reported to be a major etiological factor leading to pneumonia in the older population. It results of swallowing and cough-reflex impairments and it is significantly associated to dementia, cerebrovascular disease, Parkinson disease, Chronic obstructive pulmonary disease (COPD) and gastroesophageal reflux disease[1–5].

Aspiration Pneumonia (ASP) is a function-based category of pneumonia that is caused by the misdirection of fluids (liquids, saliva, secretions) or food with colonised pathogens into the lungs[6–8]. Its diagnosis is usually defined when there is radiological confirmation or a combination of valid clinical features of pneumonia with the simultaneous presence of risk factors and demonstrated or suspected aspiration. Three main risk factors that have been reported are: impaired safety of swallowing, which propels aspiration to the respiratory tract; impaired nutritional status, that is related with depressed immunologic responses; and poor oral health and hygiene, with respiratory pathogens colonised in the oral cavity[9,10]. Due to the lack of specific and rigorous markers of aspiration, ASP is frequently underdiagnosed[11–14].

Aspiration Pneumonia prevalence has been shown to increase with age and it is associated to high rates of hospital readmission, morbidity and in-hospital mortality, and to increased lengths of stay[2,15–17].

A recent longitudinal study conducted in acute care hospitals of the United States of America (USA) showed that between 2002 and 2012 the incidence rate of ASP was 15 times higher in older patients than in patients aged younger than 65 years; the study also showed that the hospitalisation costs for ASP almost doubled during the study period[15].

Given the burden of ASP on patients, caregivers and the healthcare system and considering that some statistically significant risk factors for ASP are considered modifiable (e.g., dysphagia, dependency for feeding, dependency for oral care, feeding tube, weight loss, multiple medications, and impaired functional status) the importance of adopting preventive strategies to reduce ASP in older adults is clear and has been extensively reported[3,7,15,17–19].

In 2003, Loeb et al.[20] systematically reviewed randomised controlled trials (RCT) which evaluated the effectiveness of preventive strategies for ASP in older people and concluded that clinical trial data available at the time was scarce. In their review, which included a total of eight studies, two of them were based on pharmacologic therapy and reported statistically significant risk reduction in pneumonia, but presented several adverse effects, including bleeding. One of the included studies had its focus on oral care, two investigated dietary interventions and compensatory strategies, and three

other articles studied enteral feeding. All of the included RCT were considered to have high risk of bias according to the authors definition[20]. To the best of our knowledge, there is no recent available update of this systematic review.

The present article reports an updated systematic review of RCT that studied the effectiveness of pharmacologic and non-pharmacologic interventions to prevent aspiration pneumonia in older adults.

2. METHOD

An update of an earlier systematic review[20] was developed using a protocol registered on PROSPERO (CRD42019139973) and conducted according with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

2.1 Eligibility Criteria

The studies that were included had to focus on the effectiveness of single or multiple interventions to prevent ASP in patients aged 65 years or older, with reported oropharyngeal dysphagia (OD), previous stroke, previous aspiration, or tube feeding. All studies had to report incidence of pneumonia as primary or secondary outcome, diagnosed by chest X-ray or recognised clinical diagnostic criteria. Conference abstracts, letters to editor, case reports, case series, literature reviews, and trials on post-operative pneumonia were excluded. Because the previous systematic review[20] analysed original RCT published until 2001, the literature search was restricted to articles with the same study design published since January 2002. Only articles written in English were included.

2.2 Search Strategy

The MEDLINE, Scopus and Web of Science databases, and the Cochrane Central Register of Controlled Trials were searched on July 23, 2019. Similar search strategies were used for all databases, combining Medical Subject Headings or free text words with the Boolean operators “AND/OR”. Search terms were “aspiration pneumonia”, “prevention and control”, “older adults”, “elderly”, “deglutition”, “swallowing”, “oral hygiene”, “compensatory strategy”, “positioning”, “pharmacologic therapy”, “rehabilitation”, “feeding”, “education”, “training”, “dietary intervention”, and “feeding tube”. Depending on the database, filters on years of publication, human trials, and study design were applied.

2.3 Study Selection

One of the reviewers (JS) performed the literature search and the screening of the results by title and abstract using broad inclusion and exclusion criteria. Screening decisions were checked by another reviewer (MM). Then, two reviewers (JS and MM) independently analysed full-text articles and decided on inclusion or exclusion by consensus. Disagreements were resolved through discussion and consensus reached with two additional reviewers (OR and LJ).

2.4 Data Synthesis

One of the authors (JS) extracted data from the included articles and created summary tables with individual characteristics of the studies. Included studies' findings were qualitatively analysed by intervention category and participants characteristics and the intervention effect was considered to be positive, negative or with no overall effect if the studies reported statistically significant decrease, increase or no effect in pneumonia incidence, respectively. This analysis was based on the statistical data provided by each study (Qui-square independence tests, logistic regressions and Kaplan-Meier survival analysis). Three reviewers (MM, OR and LJ) verified the accuracy of the data extraction and synthesis.

2.5 Methodological Quality Assessment

Two reviewers (JS and MM) independently assessed risk of bias for all included studies using Cochrane criteria[21]. Each domain was classified with low, high, or unclear risk of bias. Disagreements were discussed in a consensus meeting with two additional researchers (OR and LJ). Adequate follow-up was considered if 80% or more of the participants were still in the sample at the end of the study.

3. RESULTS

3.1 Study Selection

A total of 629 citations were found, 64 were assessed by full-text analysis and 13 met the eligibility criteria and thus included in the systematic review. Figure 1 provides a descriptive flow diagram of the selection process. The main reasons for exclusion of articles were related to study design (not RCT, abstracts and reviews), study population (paediatric, surgical patients and animals), objectives (treatment instead of preventive methods and prevalence studies), outcomes (other than pneumonia) and language the article was written in (not English). After the independent full-text study selection by two reviewers (JS and MM), different decision on eligibility was found in ten studies[22–31]. Thus, each one of them was analysed by two additional reviewers (OR and LJ) and discussed with all to reach consensus. Four of the discussed articles were excluded due to study design. Within the six included articles, four studies[29–32] had defined 18 years as minimum age for study inclusion, but it was decided to include these articles since the mean ages of the participants were between 73 and 83 years and the majority of the participants in intervention and control groups of one study[29] was older than 65 (69 and 72%, respectively). Contact was attempted, with no success, with the authors of the other two discussed studies[27,33] in order to ask for further information on the proportion of participants younger than 65 as they had not established eligibility criteria for age.

3.2 Study Characteristics

All included studies were RCT and two of them[29,30] were randomised by cluster. The main settings of the included studies were acute stroke units (ASU), general hospitals and geriatric facilities. Regarding intervention category, six of the included studies[26,30,33–36] aimed to test pharmacologic interventions, three studies[31,32,37] focused on dietary interventions or compensatory strategies, one study[27] based its intervention in the use of a specific oral hygiene product, one study[28] tested an intervention which combined both dietary intervention and oral hygiene, one study[29] analysed the effectiveness of a multidisciplinary intervention, and one study[38] focused on a rehabilitative technique. The overall characteristics of the included studies are presented in Table 1 and a descriptive summary of study components is provided in Table 2.

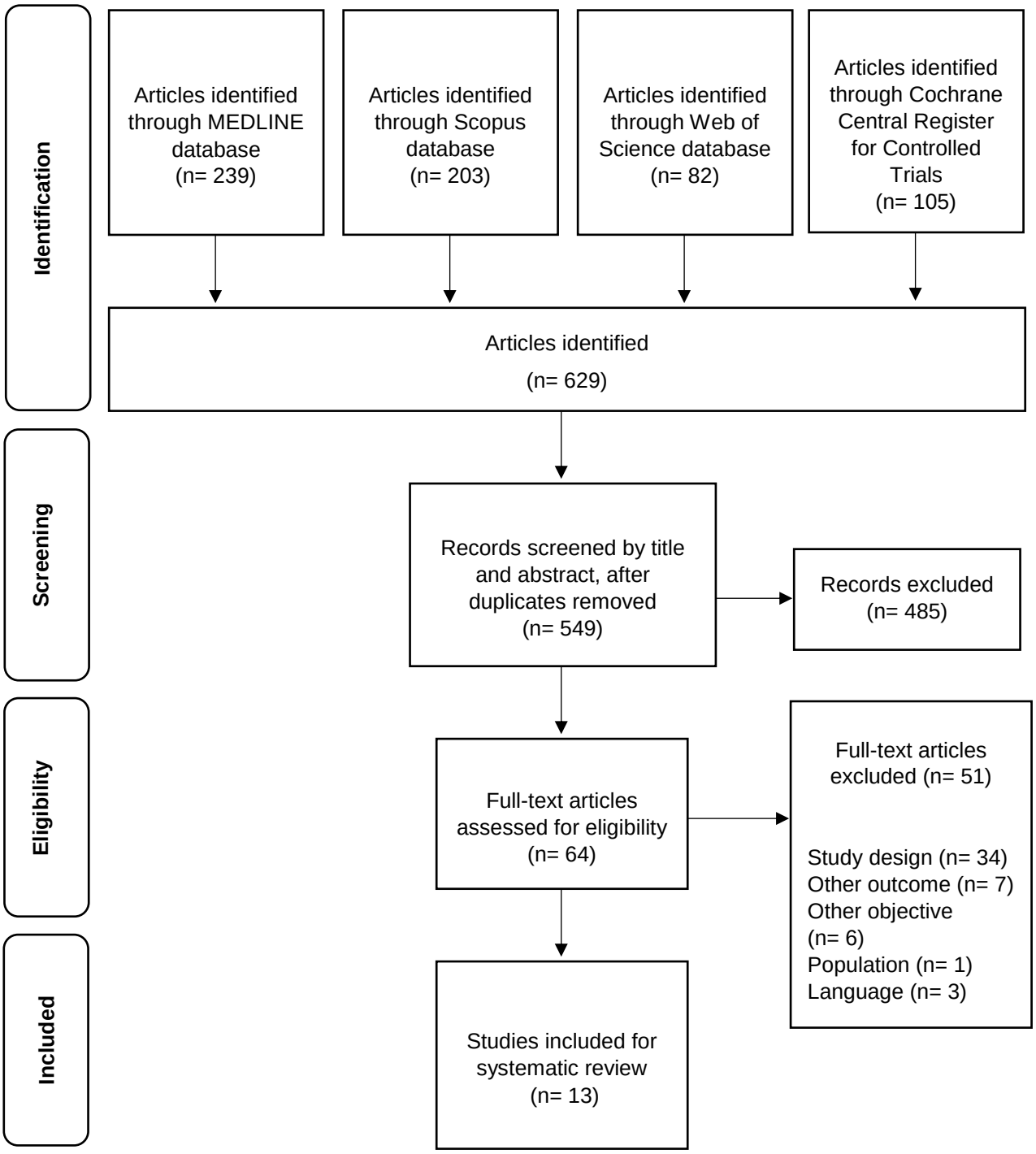

Figure 1 – Flow diagram describing the study selection process, adapted from PRISMA.

3.3 Participant Characteristics

All the participants of included studies had some level of aspiration risk. Three studies[27,29,30] included acute stroke patients, two studies[32,34] focused on older patients with neurologic diseases (dementia, Parkinson's disease and cerebrovascular disease), three studies[26,28,38] recruited older adults with dysphagia, and five studies[31,33,35–37] included patients with need for enteral nutrition (EN). A wide range of sample sizes was

observed throughout the included articles, ranging from 27 to 1126 participants. Two of the articles[27,29] did not present means of age of participants and described their population in groups of age or using median values. In Middleton *et al.*[29], the control and intervention groups younger than 65 years were composed of 28% and 31% of the participants, respectively; groups ranging from 65 to 74 years of age represented 26% and 24% of the sample (control and intervention); from 75 to 84 years of age, were 32% and 29%; and the groups aged 85 and older represented 15% and 16% of the total number of participants (control and intervention). Gosney et al.[27] divided the participants in three groups, concerning the hospital where they were admitted, and the median values of age were between 62 and 78 years, with an age range from 16 to 96 years. Further descriptive data on the participants of the included studies is synthesized in Tables 1 and 2.

Table 1 - Characteristics of Included Studies (n=13)

Study	Design	Country of origin	Participants (n)		Age, Mean (SD)		Duration of follow-up
			Intervention	Control	Intervention	Control	
Gosney, 2006[27]	RCT	UK	103	100	NR	NR	8 and 15 days
Iwasaki, 2007[34]	RCT	Japan	44	48	84.5 (6.8)	83.1 (7.2)	12 months
Robbins, 2008[32]	RCT	USA	Int. 1: 133 Int. 2: 123 Int. 3: 259	N/A	Int. 1: 80 Int. 2: 81 Int. 3: 81	N/A	3 months
Lee, 2010[37]	RCT	China	85	93	83.4 (9.4)	83.2 (9.9)	1 month
Middleton, 2011[29]	CRCT	Australia	626	500	NR	NR	90 days after ASU admission
Nakashima, 2011[26]	RCT	Japan	Imid.: 30 Nicer.: 30	N/A	Imid.: 80.0 Nicer.: 79.0	N/A	6 months
Takatori, 2013[33]	RCT	Japan	Lans.: 41 Mosa.: 38	40	Lans.: 85.0 Mosa.: 82.5	80.5	6 months
Kalra, 2015[30]	CRCT	UK	615	602	77.7 (11.9)	78.0 (12.2)	14 and 90 days
Lee, 2015[35]	RCT	China	33	38	83.4 (6.8)	84.4 (5.6)	26 weeks
Warusevitane, 2015[36]	RCT	UK	30	30	76.9 (6.3)	79.2 (10.8)	21 days
Fujimaki, 2017[38]	RCT	Japan	259	284	73.8 (7.5)	73.9 (7.0)	6 months
Higashiguchi, 2017[28]	RCT	Japan	109	143	88.3 (5.8)	87.9 (7.0)	8 months
Tabei, 2018[31]	RCT	Japan	15	12	82.7 (11.1)	82.9 (8.6)	14 days

SD, Standard deviation; RCT, Randomized controlled trial; CRCT, Cluster-randomized controlled trial; NR, Not reported; N/A, Not applicable; UK, United Kingdom; USA, United States of America.

Table 2 – Summary of Study Components

Study	Participants	Setting	Intervention	Comparison	Primary outcomes	Secondary outcomes
Gosney, 2006[27]	Patients with first acute stroke, within the first 24h of admission	ASU of three hospitals	Selective decontamination of the digestive tract with an oral gel	Placebo	Level of colonization of aerobic Gram-negative bacteria (AGNB)	Pneumonia
Iwasaki, 2007[34]	Inpatients with diagnosis of cerebrovascular disease, Parkinson's disease or Alzheimer's disease, or various combinations of the three conditions	Long-term care hospitals	2.5 g of BHT two or three times a day, depending on patients' body weight	Placebo (1.0 g of lactose)	Pneumonia and death-from pneumonia	Number of febrile days and number of days during which a patient was treated with antibiotics
Robbins, 2008[32]	Aged ≥ 50 years, with Dementia or Parkinson Disease, with suspected aspiration of liquids	Acute and subacute care units	Intervention 1: nectar-thick liquids Intervention 2: honey-thick liquids	Chin-down posture	Pneumonia (cumulative incidence rate)	Death (cumulative incidence rate)
Lee, 2010[37]	Aged ≥ 60 years, who were likely to require nasogastric tube feeding for at least 4 weeks	Three convalescence hospitals and 1 infirmary	Continuous pump feeding	Intermittent bolus feeding by gravity	Pneumonia	Death
Middleton, 2011[29]	Aged ≥ 18 years, with diagnosis of ischemic stroke or intracerebral haemorrhage, within 48h of onset of symptoms	ASU	Fever, Sugar and Swallowing Intervention (FeSS)	Abridged version of existing guidelines	Death or dependency, functional dependency, mean SF-36 mental component summary score, and mean physical component summary score	Mean temperature and mean finger-prick blood glucose for the first 72h after ASU admission, proportion with swallowing screening undertaken within the first 24h of ASU admission, discharge diagnosis of aspiration pneumonia and length of hospital stay

Nakashima, 2011[26]	Aged ≥ 65 years, with history of pneumonia within the previous 2 years and presence of dysphagia	General hospital	Imidapril group: 5mg of imidapril daily	Nicergoline group: 15mg of nicergoline daily	Serum levels of substance P	Pneumonia recurrence
Takatori, 2013[33]	Patients with dysphagia who required gastrostomy feeding	Geriatric hospitals and nursing facilities	Lansoprazole group: 15mg lansoprazole once a day via PEG tube before morning meal; Mosapride group: 5mg of mosapride citrate 3 times a day via PEG tube before each meal	No medication	Pneumonia	Days of fever and days of vomiting
Kalra, 2015[30]	Aged ≥ 18 years, with confirmed diagnosis of acute stroke, with onset of symptoms within 48h at recruitment, and failed bedside swallow test or presence of nasogastric tube	Stroke units	Prophylactic antibiotics for 7 days plus standard stroke unit care	Standard stroke unit care	Pneumonia	Death at 14 and 90 days, functional status at 90 days, length of stay, CDT-positive diarrhoea, MRSA colonization, health-related quality of life (EuroQoL)
Lee, 2015[35]	Tube-fed patients, aged ≥ 60 years, with history of recent hospitalization in the previous 3 months, and that had been on tube-feeding for more than 2 weeks because of neurologic dysphagia, with clinical diagnosis of cerebrovascular diseases	Acute university medical wards, subacute hospitals, affiliated geriatric outpatient clinics and speech therapy clinics	Lisinopril 2,5mg once daily at bedtime	Placebo	Pneumonia (incidence rate)	Death and fatal pneumonia (incidence rates)
Warusevitane, 2015[36]	Patients within 7 days of acute ischemic or haemorrhagic stroke confirmed by CT scan, who required NGT for >24 hours, and could be	ASU	10 mg metoclopramide (10 mL), 3 times daily via the NGT	Placebo (10 mL normal saline)	Pneumonia	Witnessed aspiration, highest levels of white blood cell count and C-reactive protein, the lowest oxygen

	recruited within 48 hours of NGT insertion					saturation, the number of antibiotic days, neurological deficits, swallow improved and NGT removed/referral for PEG
Fujimaki, 2017[38]	Patients aged ≥ 60 years, complaining of aspiration or hoarseness/dysphonia caused by glottal incompetence, and endoscopically confirmed	General hospitals	Self-controlled vocal exercise guided by a DVD	Control patients were given an informative brochure with explanations and recommendations	Maximum phonation time	Hospitalizations with pneumonia
Higashiguchi, 2017[28]	Patients at risk for aspiration pneumonia, aged ≥ 75 years, BMI < 18.5kg/m2, serum albumin level ≤ 3.5g/dL, with dysphagia but had capacity for oral food intake, with thickening agent for drinks	1: intensive care home for the older people; 2: nursing care facility for older people; 3: rehabilitation hospital	Oral care intervention (wiping) and oral nutritional supplements (ONS)	Conventional oral care and diet	Pneumonia	Body weight, crural circumference, mean daily caloric intake and blood biochemistry parameters
Tabei, 2018[31]	Aged ≥ 20 years, who needed nutritional therapy intervention because oral intake was not possible for any reason, who received EN management limited to the stomach	General hospitals	Viscosity-regulating pectin solution administered as a bolus using a syringe in patients before the administration of the liquid EN diet	Liquid EN diet administered to patients based on the conventional method in each participating institution	Pneumonia, fever over 37.5˚C and vomiting	Onset of diarrhoea, infusion period (time)

ASU, Acute Stroke Unit; CDT, Clostridium difficile toxin; MRSA, methicillin-resistant Staphylococcus aureus; PEG, Percutaneous endoscopic gastrostomy; SF-36 Health Survey; NGT, Nasogastric tube; EN, Enteral nutrition.

3.4 Summary of Findings

Table 3 summarises reported data on the effectiveness of the interventions of all included studies.

3.4.1 Pharmacologic Therapy

Six studies[26,30,33–36] focused on pharmacologic therapy interventions, in which three studies[33,35,36] addressed older adults who required EN, and other three studies[26,30,34] enrolled older patients with neurologic disease (stroke, dementia or Parkinson's disease).

Regarding the first three articles[33,35,36], one study[36] evaluated the effect of regular treatment with metoclopramide (10mg; three times daily) on the incidence of pneumonia in nasogastric tube (NGT)-fed patients. The results showed a significant decrease of pneumonia in the intervention group when compared to the placebo group (OR, 5.24; p<0.001). Regarding mortality, there were also fewer deaths in metoclopramide group, but no statistically significant effect was attained (OR, 1.85; p=0.292). Diarrhoea was the most common side-effect within the participants (20% in the placebo group and 30% in the intervention group; p=0.371). Other study[33] assessed the therapeutic effect of mosapride citrate and lansoprazole on the prevention of ASP in patients receiving percutaneous endoscopic gastrostomy (PEG) feeding, based on the premises that the anti-reflux effect of mosapride and the lowering of intragastric acidity and fluid volume powered by lansoprazole might prevent ASP in these patients. The study results showed a significant reduction of pneumonia in the mosapride group when compared with control (p=0.038) and lansoprazole (p=0.005) groups. The authors[33] did not provide statistical analysis of the comparison between lansoprazole and control groups; and no adverse effects were reported. Another RCT[35] was conducted in order to assess if angiotensin enzyme converting (ACE) inhibitors (lisinopril; 2.5mg/day) reduce the incidence of pneumonia in tube-fed frail older patients with severe dysphagia due to cerebrovascular disease. The study results showed similarly high incidence of pneumonia in both ACE inhibitor and control groups (p=0.390); and higher mortality rate in the intervention group participants (OR 7.79; p=0.018).

Within the other three articles, one study[34] analysed the effectiveness of the traditional Chinese herbal medicine Banxia Houpu Tang (BHT) for preventing ASP and pneumonia-related mortality in older adults; and the study findings pointed to significantly lower rate of pneumonia in BHT group as compared with control group (p=0.008). No adverse events were observed among the study participants. A second study[26] compared the effects of nicergoline (5mg/day) on serum substance P, dysphagia and

pneumonia recurrence with the effects of imidapril (15mg/day) in older adults with dysphagia and previous history of pneumonia, but there was no statistically significant difference in the pneumonia recurrence between both interventions. Neither of the groups presented side-effects during the trial period. A third study[30] aimed to assess the effectiveness of prophylactic antibiotics for reducing pneumonia and mortality in patients with dysphagia after acute stroke; and its results revealed no significant differences in both outcomes between the groups (pneumonia OR 1.21, p=0.489; mortality OR 0.95, p=0.796).

3.4.2 Dietary Intervention and Compensatory Strategy

Two studies[31,32] analysed the effect on pneumonia of interventions based on the adaptation of food consistencies and one study[37] compared the effectiveness of two different formula delivery modes among tube-fed older patients. Other study[28] used oral nutrition supplementation as part of an oral hygiene intervention and it is approached in *Multidisciplinary Intervention* category.

Robbins et al.[32] performed a 3-month RCT to compare the effectiveness of chin-down posture and two consistencies of thickened liquids on the cumulative incidence rate of pneumonia in older patients with dementia or Parkinson's disease. The results showed no statistically significant differences in the survival analysis between the thickened liquid and chin-down groups, and neither between nectar-thick and honey-thick liquid groups (Table 3). The main adverse events experienced by the participants were dehydration, urinary tract infection and fever, and their incidence was higher in the thickened liquids groups than in the chin-down group.

Two studies[31,37] conducted RCT focused on compensatory strategies for older patients who required EN. Lee *et al.*[37] compared the effect on pneumonia from two formula delivery modes (intermittent bolus feeding by gravity and continuous pump feeding) and the results showed no statistically significant differences in pneumonia and mortality between groups. The authors[37] reported no adverse events. Tabei et al.[31] assessed the effectiveness of a viscosity-regulating pectin solution in EN management when compared with the conventional liquid EN diet administration. No significant differences were observed regarding pneumonia between the two groups, as none of the participants presented pneumonia during the study period. Likewise, no adverse events were observed.

3.4.3 Oral Hygiene

Two studies[27,28] explored oral care interventions and one of them combined oral hygiene with nutritional supplementation, so it is described below in the category of *Multidisciplinary Intervention*. In 2006, Gosney et al.[27] conducted a RCT to investigate the effectiveness of selective decontamination of the digestive tract (SDD) with a specific oral gel on the morbidity and mortality of patients with acute stroke. The study was developed in the ASU of three hospitals in England, included 100 patients for the intervention group and 103 for control and follow-up assessments were made at days 8 and 15. The study results suggested a positive and statistically significant effect of SDD intervention in reducing the incidence of pneumonia in acute stroke patients (p=0.029). In what concerned mortality, 11% of the deaths were in the control group and 9% in the intervention group, but the authors failed to report data on the statistical significance of these results. No adverse events associated to this intervention were reported.

3.4.4 Multidisciplinary intervention

Two articles addressed multidisciplinary interventions. One study[28] evaluated the effectiveness of a combined care intervention, which was composed of oral hygiene and oral nutritional supplements, on the incidence of pneumonia in adults aged 75 or older. Intervention consisted in providing oral care intervention (wiping) and oral nutritional supplements in addition to the usual oral care and diet of the participating facilities. The results of the study showed no statistically significant differences in the incidence of pneumonia at follow-up, although it was higher in the control group than in the intervention group (p=0.056). The authors pointed out the significantly higher prevalence of swallowing dysfunction at baseline in the intervention group (p=0.009) as a possible constraint to the demonstration of significance on the expected outcome. However, the results showed a significant increase in the body weight of the intervention group and the authors underlined this as an important aspect for further study regarding the prevention of sarcopenia in older adults. No adverse events associated to the intervention were reported.

Another study[29] reported the implementation of the Quality in Acute Stroke Care (QASC) program in a cluster-randomised controlled trial that aimed to assess the effect of multidisciplinary team building workshops and a standardised education program to implement evidence-based treatment protocols on the management of fever, hyperglycaemia and swallowing dysfunction in acute stroke patients. Regarding swallowing, nurses had to successfully complete an education program on dysphagia screening and all patients admitted for acute stroke had to be screened for dysphagia

within the first 24 hours. Patients who failed the swallowing screening were referred to a speech pathologist for clinical assessment. At follow-up, no statistically significant differences were found in the prevalence of ASP between intervention and control groups (p=0.82). However, patients in the intervention group were significantly more likely to be alive and independent at the end of the study period (p=0.002). Given these results, the authors underlined the importance of multidisciplinary triage and early intervention in acute stroke patients for the reduction of rates of death and dependency and for the improvement of processes of care.

3.4.5 Rehabilitative interventions

One six-month RCT[38] was conducted to assess the effectiveness of a self-controlled vocal exercise on the incidence of pneumonia in older patients with physiological glottal closure. The authors reported statistically significant differences between the intervention and the control groups regarding the incidence of hospitalisations with pneumonia (0.77 and 6.34%, respectively; p<0.001). During the clinical trial period, three participants presented hyperadduction of the false vocal folds as an adverse effect of the intervention, but it was resolved in all subjects with exercise performance correction[38]. Since vocal function significantly improved in the intervention group and the incidence of pneumonia was significantly lower than in control group, authors suggested that this new technique might be a cost-effective method for preventing pneumonia in older adults with presbyphonia.

3.5 Methodological Quality

Based on the Cochrane Collaboration's tool for assessing risk of bias[21], one study[35] was considered to have low overall risk of bias, three articles[27,37,38] were classified with high overall risk of bias, and the remaining nine studies[26,28–34,36] raised doubts about one or more domains and therefore were considered as having unclear overall risk of bias. The degree of agreement between the two reviewers on the risk of bias assessment ranged from 61.5 to 100%.

Regarding follow-up, all the studies had over 80% of the participants at the end of the study period and were considered to have adequate follow-up, except for three studies[28,35,38].

The consensus decisions on the methodological quality and follow-up adequacy of the included studies are presented in Table 4.

Table 3 – Effectiveness of Interventions Described in the Included Studies

Study	Pneumonia		P-value	Effect	Death		P-value	Adverse effects
	Intervention	Control			Intervention	Control		
Gosney, 2006[27]	0.97%	7%	0.029	+	8.74%	11%	NR	NR
Iwasaki, 2007[34]	9.1%	29.20%	0.008	+	RR 0.41 (95% CI 0.10, 1.03) [a]		0.06	None
Robbins, 2008[32]	HR 0.84 (95% CI 0.49, 1.45) [b] HR 0.50 (95% CI 0.23, 1.09) [c]	N/A	0.530 [b] 0.083 [c]	<>	HR 0.98 (95% CI 0.65, 1.48) [d] HR 0.76 (95% CI 0.43, 1.36) [e]	N/A	0.940 [d] 0.360 [e]	Dehydration, urinary tract infection, fever *
Lee, 2010[37]	14.10%	15.10%	NR	<>	8.20%	14.0%	0.226	NR
Middleton, 2011[29]	2.16%	2.69%	0.820	<>	24.78%	38.59%	0.020	NR
Nakashima, 2011[26]	Imid.: 30% Nicer.: 17%	N/A	NR	<>	NR	N/A	NR	None
Takatori, 2013[33]	Lans.: 49% Mosa.: 18%	40%	0.038 [f]	+	NR	NR	NR	NR
Kalra, 2015[30]	OR 1.21 (95% CI 0.71, 2.08) [g]		0.489	<>	OR 0.95 (95% CI 0.62, 1.44) [h]		0.796	Non-post-stroke pneumonia infections (p=0.02) **
Lee, 2015[35]	57.60%	47.40%	0.390	<>	OR 7.79 (95% CI 1.42, 42.65) [i]		0.020	NR
Warusevitane, 2015[36]	OR 5.24 (95% CI 2.43, 11.27) [j]		<0.001	+	OR 1.85 (95% CI 0.59, 5.80) [k]		0.292	Diarrhoea
Fujimaki, 2017[38]	0.77%	6.34%	<0.001	+	NR	NR	NR	Hyperadduction of the false vocal folds
Higashiguchi, 2017[28]	7.8%	17.7%	0.056	<>	NR	NR	NR	NR
Tabei, 2018[31]	0	0	N/A	N/A	NR	NR	NR	None

OR, Odds Ratio; CI, Confidence interval; NR, Not reported; N/A, Not applicable; Effect: (+) positive effect, (<>) no effect, (-) negative effect; [a] Relative risk of death from pneumonia adjusted for facility; [b] Results from the 3-month Kaplan-Meier estimates of pneumonia in the chin-down posture and thickened-liquid groups; [c] Results from the 3-month Kaplan-Meier estimates of pneumonia in the nectar-thick and honey-thick liquid groups; [d] Results from the 3-month Kaplan-Meier estimates of pneumonia or death in the chin-down posture and thickened-liquid groups; [e] Results from the 3-month Kaplan-Meier estimates of pneumonia or death in the nectar-thick and honey-thick liquid groups; [f] Control vs. Mosapride; [g] Results from odds ratio of post-stroke pneumonia at 14 days, adjusted for patient, stroke, and centre characteristics; [h] Results from odds ratio of all-cause mortality at 14 days; [i] Results from odds ratio of 6-month mortality, adjusted for all baseline characteristics of Intervention and Placebo Groups; [j] Results from the between-group rate ratio of pneumonia, adjusted for age and baseline National Institutes for Health Stroke Scale score and expressed with the placebo group as the reference group; [k] Results from the between-group rate ratio of deaths, adjusted for age and baseline National Institutes for Health Stroke Scale score and expressed with the placebo group as the reference group; * The combined outcome of at least 1 dehydration, urinary tract infection, or fever event was significantly more frequent in the thickened-liquid groups than the chin-down posture group (p=0,055); ** Intervention group had a significantly lower number of non-post-stroke pneumonia infections compared with control.

Table 4 – Methodological Quality of the Included Studies

Study	Random Sequence Generation	Allocation Concealment	Selective Reporting	Other bias	Blinding		Incomplete outcome data	Overall risk of bias (within studies)	Follow-up
					Participants and personnel	Outcome assessors			
Gosney, 2006[27]	low	unclear	high	unclear	unclear	unclear	high	high	+
Iwasaki, 2007[34]	low	unclear	low	unclear	unclear	Low	unclear	unclear	+
Robbins, 2008[32]	low	low	unclear	unclear	unclear	unclear	low	unclear	+
Lee, 2010[37]	low	unclear	unclear	unclear	unclear	High	unclear	high	+
Middleton, 2011[29]	low	low	low	Low	unclear	Low	low	unclear	+
Nakashima, 2011[26]	low	low	low	unclear	unclear	Low	low	unclear	+
Takatori, 2013[33]	low	unclear	unclear	unclear	unclear	unclear	low	unclear	+
Kalra, 2015[30]	low	low	unclear	Low	low	Low	low	unclear	+
Lee, 2015[35]	low	low	low	Low	low	Low	low	low	-
Warusevitane, 2015[36]	low	low	Low	Low	unclear	Low	low	unclear	+
Fujimaki, 2017[38]	low	unclear	Low	unclear	unclear	High	unclear	high	-
Higashiguchi, 2017[28]	low	unclear	Unclear	unclear	unclear	unclear	unclear	unclear	NR
Tabei, 2018[31]	unclear	unclear	Low	unclear	unclear	unclear	low	unclear	+
% of agreement attained between reviewers' judgements	100	69.23	61.54	84.62	69.23	100	76.92		

Follow-up: (+) adequate; (-) inadequate; NR, not reported.

4. DISCUSSION

The aim of this review was to provide the most updated evidence on the effects of healthcare interventions to reduce ASP in older adults. Regarding the intervention types, six studies[26,30,33–36] were focused on pharmacologic therapies, three articles[31,32,37] studied dietary interventions and compensatory strategies, one[27] explored an oral hygiene intervention, two[28,29] analysed multidisciplinary approaches, and one[38] analysed a rehabilitative intervention. Five[31,33,35–37] studies analysed patients with need for EN, three articles[27,29,30] studied individuals with acute stroke, another three[26,28,38] focused on older adults with OD and risk of ASP, and two studies[32,34] considered older patients with neurodegenerative diseases. There was a wide range of sample sizes and of trial duration periods, but most studies presented small sample sizes and short-term intervention periods. As expected, the heterogeneity of the included studies did not enable a quantitative assessment of the effects.

In what concerned pharmacologic interventions, three studies[33,34,36] showed positive and statistically significant effects on pneumonia incidence. One RCT[36] analysed the use of metoclopramide in NGT-fed patients, another article[33] studied the effect of mosapride citrate in patients with PEG feeding and another study[34] assessed the effect of the traditional Chinese medicine BHT. However, the same three studies were considered as having unclear overall risk of bias, and considering the small sample sizes used, their results may not be generalisable to the population.

Regarding dietary interventions and compensatory strategies, none of the included studies[31,32,37] showed significant effect on the prevention of ASP. The use of thickened liquids, which is frequently recommended in clinical practice, remains poorly supported by RCT and one of the included studies[32] revealed that the thickened liquid group presented higher prevalence of dehydration, fever and urinary tract infections than the chin-down posture group. Thus, these effects must be considered when making decisions on the best feeding consistency for the patients at risk for ASP.

One unexpected result was the inclusion of only one RCT[27] with focus on oral care interventions, given the extensive scientific evidence supporting poor oral health as a key risk factor for developing ASP[12,17,39]. This study showed a statistically significant reduction on ASP incidence in patients with acute stroke with the use of an SDD gel. However, it was considered to have weak methodological quality and high overall risk of bias which might have led to overestimated results.

Two studies[28,29] on multidisciplinary interventions failed to demonstrate statistically significant effects on the prevention of ASP. Nevertheless, one RCT[29] showed positive effects on mortality and functionality of patients in the intervention group

which reinforced the importance of multidisciplinary interventions to improve healthcare services. Another study[28] revealed significant positive effects on body weight of the intervention group participants and the authors underlined the potential of such intervention to reduce sarcopenia in older adults.

In what concerns rehabilitative interventions, one RCT[38] met the inclusion criteria of this review and showed positive and statistically significant effect of a self-controlled vocal exercise on ASP incidence. This intervention was presented as a cost-effective technique to prevent ASP and its side-effects were shown to be reversible. In what regards to the study's methodological quality, it was considered to have high overall risk of bias mainly due to the unblinding of outcome assessors.

Of all included studies, only one RCT[35] was considered as having low overall risk of bias, but its results showed no significant effect in the prevention of ASP. The pharmacologic intervention the study considered was based on the daily administration of lisinopril to tube-fed stroke patients and revealed statistically significant reduction in the mortality of the intervention group when compared to control group (placebo).

Comparing the current review findings with those of the previous systematic review[20], there was an increase in the number of RCT conducted about this topic, since it included a total of eight articles. Regarding the intervention types, two studies were focused on pharmacologic interventions, other two on dietary interventions and compensatory strategies, one article assessed an oral hygiene method, and three RCT analysed the effects of EN. In what concerned participants phenotypes, the previous review included four studies focused on older patients with stroke or other neurologic disease, two were limited to hospitalised patients receiving EN, and one studied only nursing home residents. Four studies showed positive effect in reducing ASP, however, all the included studies presented weak methodological quality and were classified as at high risk of bias. Most studies in the previous review had small sample sizes as in the present review, but the duration of the interventions was wider, ranging from 7 days to three years. The main results of the review[20] led the authors to conclude that none of the interventions were likely to be widespread accepted in clinical practice, considering that some presented gastrointestinal and neurological side-effects and bleeding. Also, it was underlined the necessity to develop more well-designed clinical trials on this subject.

4.1 Study limitations and implications for practice

The main limitations of the present review regard the eligibility criteria (inclusion of studies with some participants younger than 65 years) preestablished in the review protocol, and to the achievement of modest overall inter-rater agreement in the

methodological assessment. Despite the Cochrane Collaboration's tool for assessing risk of bias being recognised as a useful and valid instrument to address main sources of bias in RCT and to identify studies that may exaggerate treatment effects, some evaluation studies[40,41] have reported that it also allows substantial variation in agreement between assessors across domains. Similarly to these studies results, selective reporting was the domain with the slightest inter-rater agreement[40,41].

Due to weak methodological quality across studies, small sample sizes, and the specific characteristics of the participants and the review limitations, it was not possible to draw solid conclusions on the effectiveness of the interventions reviewed for the prevention of ASP.

4.2 Future work

During the study selection, many of the identified studies that focused on the prevention of ASP were excluded because of study design (n=31). Also, there were promising results on the preventive effect of three pharmacologic interventions[33,34,36], which lead to the need for developing more and larger RCT on this subject.

5. CONCLUSIONS

Aspiration pneumonia is highly prevalent in the older population, even though it is frequently underdiagnosed. The increase of life expectancy, the high prevalence of chronic diseases in older adults and the consequent increase of functional dependency, make older people more vulnerable for developing ASP and increase the need for specialized healthcare services. Consequently, it increases the responsibilities of healthcare providers on its management. Thus, considering the negative impact of ASP in the quality of life of older patients, their families and on the sustainability of healthcare systems, the need to provide guidelines for better clinical practice is warranted[8,42–44].

The present Thesis aimed to review the most updated evidence on ASP prevention; however, in the absence of large well-designed trials with positive effects on the reduction of ASP, it is not possible to point out effective strategies that could be generalised to a specific population. Thus, the necessity of developing larger and higher-quality RCT to assess preventive interventions for ASP (already identified in 2003 by the authors of the previous review[20]), remains current.

6. REFERENCES

1. Teramoto S, Yoshida K, Hizawa N. Update on the pathogenesis and management of pneumonia in the elderly-roles of aspiration pneumonia. *Respir Investig*. 2015;53(5):178-184. doi:10.1016/j.resinv.2015.01.003
2. Miyashita N, Yamauchi Y. Bacterial Pneumonia in Elderly Japanese Populations. *Japanese Clin Med*. 2018;9:117967071775143. doi:10.1177/1179670717751433
3. Langmore SE, Skarupski KA, Park PS, Fries BE. Predictors of aspiration pneumonia in nursing home residents. *Dysphagia*. 2002;17(4):298-307. doi:10.1007/s00455-002-0072-5
4. Akbar U, Dham B, He Y, et al. Incidence and mortality trends of aspiration pneumonia in Parkinson's disease in the United States, 1979-2010. *Park Relat Disord*. 2015;21(9):1082-1086. doi:10.1016/j.parkreldis.2015.06.020
5. Wada H, Nakajoh K, Satoh-Nakagawa T, et al. Risk factors of aspiration pneumonia in Alzheimer's disease patients. *Gerontology*. 47(5):271-276. doi:10.1159/000052811
6. Marik PE. Aspiration Pneumonitis and Aspiration Pneumonia. *N Engl J Med*. 2001;344(9):665-671. doi:10.1056/nejm200103013440908
7. Ebihara S, Sekiya H, Miyagi M, Ebihara T, Okazaki T. Dysphagia, dystussia, and aspiration pneumonia in elderly people. *J Thorac Dis*. 2016;8(3):632-639. doi:10.21037/jtd.2016.02.60
8. Janssens JP, Krause KH. Pneumonia in the very old. *Lancet Infect Dis*. 2004;4(2):112-124. doi:10.1016/S1473-3099(04)00931-4
9. Martín A, Ortega O, Roca M, Arús M, Clavé P. Effect of A Minimal-Massive Intervention in Hospitalized Older Patients with Oropharyngeal Dysphagia: A Proof of Concept Study. *J Nutr Health Aging*. 2018;22(6):739-747. doi:10.1007/s12603-018-1043-3
10. Ortega O, Sakwinska O, Combremont S, et al. High prevalence of colonization of oral cavity by respiratory pathogens in frail older patients with oropharyngeal dysphagia. *Neurogastroenterol Motil*. 2015;27(12):1804-1816. doi:10.1111/nmo.12690
11. Reza Shariatzadeh M, Huang JQ, Marrie TJ. Differences in the features of aspiration pneumonia according to site of acquisition: Community or continuing care facility. *J Am Geriatr Soc*. 2006;54(2):296-302. doi:10.1111/j.1532-5415.2005.00608.x
12. van der Maarel-Wierink CD, Vanobbergen JNO, Bronkhorst EM, Schols JMGA,

de Baat C. Risk Factors for Aspiration Pneumonia in Frail Older People: A Systematic Literature Review. *J Am Med Dir Assoc*. 2011;12(5):344-354. doi:10.1016/j.jamda.2010.12.099

13. Akgün KM, Crothers K, Pisani M. Epidemiology and management of common pulmonary diseases in older persons. *Journals Gerontol - Ser A Biol Sci Med Sci*. 2012;67 A(3):276-291. doi:10.1093/gerona/glr251
14. Hollaar V, Van Der Maarel-Wierink C, Van Der Putten GJ, Van Der Sanden W, De Swart B, De Baat C. Defining characteristics and risk indicators for diagnosing nursing home-acquired pneumonia and aspiration pneumonia in nursing home residents, using the electronically-modified Delphi Method. *BMC Geriatr*. 2016;16(1):1-10. doi:10.1186/s12877-016-0231-4
15. Wu CP, Chen YW, Wang MJ, Pinelis E. National trends in admission for aspiration pneumonia in the United States, 2002-2012. *Ann Am Thorac Soc*. 2017;14(6):874-879. doi:10.1513/AnnalsATS.201611-867OC
16. Teramoto S, Fukuchi Y, Sasaki H, et al. High incidence of aspiration pneumonia in community- and hospital-acquired pneumonia in hospitalized patients: a multicenter, prospective study in Japan. *J Am Geriatr Soc*. 2008;56(3):577-579. doi:10.1111/j.1532-5415.2008.01597.x
17. Langmore SE, Terpenning MS, Schork A, et al. Predictors of aspiration pneumonia: How important is dysphagia? *Dysphagia*. 1998;13(2):69-81. doi:10.1007/PL00009559
18. Quagliarello V, Ginter S, Han L, Van Ness P, Allore H, Tinetti M. Modifiable risk factors for nursing home-acquired pneumonia. *Clin Infect Dis*. 2005;40(1):1-6. doi:10.1086/426023
19. Pick N, McDonald A, Bennett N, et al. Pulmonary aspiration in a long-term care setting: Clinical and laboratory observations and an analysis of risk factors. *J Am Geriatr Soc*. 1996;44(7):763-768. doi:10.1111/j.1532-5415.1996.tb03731.x
20. Loeb MB, Becker M, Eady A, Walker-Dilks C. Interventions to prevent aspiration pneumonia in older adults: a systematic review. *J Am Geriatr Soc*. 2003;51(7):1018-1022. doi:10.1046/j.1365-2389.2003.51318.x
21. Higgins JPT, Altman DG, Sterne JAC. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (Updated March 2011)*. The Cochrane Collaboration; 2011. www.handbook.cochrane.org.
22. Yoneyama T, Yoshida M, Ohrui T, et al. Oral care reduces pneumonia in older patients in nursing homes. *J Am Geriatr Soc*. 2002;50(3):430-433.

doi:10.1046/j.1532-5415.2002.50106.x

23. Ueda K, Yamada Y, Toyosato A, Nomura S, Saitho E. Effects of functional training of dysphagia to prevent pneumonia for patients on tube feeding. *Gerodontology*. 2004;21(2):108-111. http://www.ncbi.nlm.nih.gov/pubmed/15185991. Accessed October 14, 2019.
24. Adachi M, Ishihara K, Abe S, Okuda K, Ishikawa T. Effect of professional oral health care on the elderly living in nursing homes. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 2002;94(2):191-195. doi:10.1067/moe.2002.123493
25. Sharif-Abdullah SSB, Chong MC, Surindar-Kaur SS, Kamaruzzaman SB, Ng KH. The effect of chlorhexidine in reducing oral colonisation in geriatric patients: a randomised controlled trial. *Singapore Med J*. 2016;57(5):262-266. doi:10.11622/smedj.2016091
26. Nakashima T, Hattori N, Okimoto M, Yanagida J, Kohno N. Nicergoline improves dysphagia by upregulating substance p in the elderly. *Medicine (Baltimore)*. 2011. doi:10.1097/MD.0b013e318224413b
27. Gosney M, Martin M V, Wright AE. The role of selective decontamination of the digestive tract in acute stroke. *Age Ageing*. 2006;35(1):42-47. doi:10.1093/ageing/afj019
28. Higashiguchi T, Ohara H, Kamakura Y, et al. Efficacy of a New Post-Mouthwash Intervention (Wiping Plus Oral Nutritional Supplements) for Preventing Aspiration Pneumonia in Elderly People: A Multicenter, Randomized, Comparative Trial. *Ann Nutr Metab*. 2017;71(3-4):253-260. doi:10.1159/000485044
29. Middleton S, McElduff P, Ward J, et al. Implementation of evidence-based treatment protocols to manage fever, hyperglycaemia, and swallowing dysfunction in acute stroke (QASC): A cluster randomised controlled trial. *Lancet*. 2011. doi:10.1016/S0140-6736(11)61485-2
30. Kalra L, Irshad S, Hodsoll J, et al. Prophylactic antibiotics after acute stroke for reducing pneumonia in patients with dysphagia (STROKE-INF): A prospective, cluster-randomised, open-label, masked endpoint, controlled clinical trial. *Lancet*. 2015. doi:10.1016/S0140-6736(15)00126-9
31. Tabei I, Tsuchida S, Akashi T, et al. Effects of a novel method for enteral nutrition infusion involving a viscosity-regulating pectin solution: A multicenter randomized controlled trial. *Clin Nutr ESPEN*. 2018. doi:10.1016/j.clnesp.2017.11.005
32. Robbins J, Gensler G, Hind J, et al. Comparison of 2 interventions for liquid aspiration on pneumonia incidence: a randomized trial. *Ann Intern Med*. 2008;148(7):509-518. doi:10.7326/0003-4819-148-7-200804010-00007

33. Takatori K, Yoshida R, Horai A, et al. Therapeutic effects of mosapride citrate and lansoprazole for prevention of aspiration pneumonia in patients receiving gastrostomy feeding. *J Gastroenterol*. 2013. doi:10.1007/s00535-012-0725-6
34. Iwasaki K, Kato S, Monma Y, et al. A pilot study of Banxia Houpu Tang, a traditional Chinese medicine, for reducing pneumonia risk in older adults with dementia. *J Am Geriatr Soc*. 2007;55(12):2035-2040. doi:10.1111/j.1532-5415.2007.01448.x
35. Lee JSW, Chui PY, Ma HM, et al. Does Low Dose Angiotensin Converting Enzyme Inhibitor Prevent Pneumonia in Older People With Neurologic Dysphagiae-A Randomized Placebo-Controlled Trial. *J Am Med Dir Assoc*. 2015;16(8):702-707. doi:10.1016/j.jamda.2015.05.009
36. Warusevitane A, Karunatilake D, Sim J, Lally F, Roffe C. Safety and effect of metoclopramide to prevent pneumonia in patients with stroke fed via nasogastric tubes trial. *Stroke*. 2015;46(2):454-460. doi:10.1161/STROKEAHA.114.006639
37. Lee JSW, Kwok T, Chui PY, et al. Can continuous pump feeding reduce the incidence of pneumonia in nasogastric tube-fed patients? A randomized controlled trial. *Clin Nutr*. 2010. doi:10.1016/j.clnu.2009.10.003
38. Fujimaki Y, Tsunoda K, Kobayashi R, et al. Independent exercise for glottal incompetence to improve vocal problems and prevent aspiration pneumonia in the elderly: A randomized controlled trial. *Clin Rehabil*. 2017. doi:10.1177/0269215516673208
39. Awano S, Ansai T, Takata Y, et al. Oral health and mortality risk from pneumonia in the elderly. *J Dent Res*. 2008;87(4):334-339. doi:10.1177/154405910808700418
40. Savović J, Weeks L, Sterne JAC, et al. Evaluation of the Cochrane Collaboration's tool for assessing the risk of bias in randomized trials: focus groups, online survey, proposed recommendations and their implementation. *Syst Rev*. 2014;3:37. doi:10.1186/2046-4053-3-37
41. Hartling L, Ospina M, Liang Y, et al. Risk of bias versus quality assessment of randomised controlled trials: Cross sectional study. *BMJ*. 2009;339(7728):1017. doi:10.1136/bmj.b4012
42. Lanspa MJ, Jones BE, Brown SM, Dean NC. Mortality, morbidity, and disease severity of patients with aspiration pneumonia. *J Hosp Med*. 2013;8(2):83-90. doi:10.1002/jhm.1996
43. Taylor JK, Fleming GB, Singanayagam A, Hill AT, Chalmers JD. Risk factors for aspiration in community-acquired pneumonia: Analysis of a hospitalized UK

cohort. *Am J Med*. 2013;126(11):995-1001. doi:10.1016/j.amjmed.2013.07.012

44. Komiya K, Rubin BK, Kadota JI, et al. Prognostic implications of aspiration pneumonia in patients with community acquired pneumonia: A systematic review with meta-analysis. *Sci Rep*. 2016;6(June):1-2. doi:10.1038/srep38097

ANNEX I – Systematic review protocol

Interventions to prevent aspiration pneumonia in older adults: an updated systematic review

Joana Santos, Óscar Ribeiro, Luis Jesus, Maria Matos

Citation

Joana Santos, Óscar Ribeiro, Luis Jesus, Maria Matos. Interventions to prevent aspiration pneumonia in older adults: an updated systematic review. PROSPERO 2019 CRD42019139973 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019139973

Review question

What is the effectiveness of pharmacologic therapies, rehabilitation techniques, compensatory strategies/positioning changes, dietary interventions, educational programs, oral hygiene and tube feeding for prevention of aspiration pneumonia in older adults?

Searches

The search will be performed using the following databases: MEDLINE (PubMed), Cochrane Library, Scopus and Web of Science. The search terms will include the Medical Subject Heading (MeSH Terms) “aspiration pneumonia” with the qualifier “prevention and control” combined with the free-text words “older adults”, “elderly”, “deglutition”, “oral hygiene”, “compensatory strategy”, “positioning”, “pharmacologic therapy”, “rehabilitation”, “feeding”, “education”, “training”, “dietary intervention” and “feeding tube”. Only articles written in English and published from January 2002 to June 2019 will be included.

Types of study to be included

Only original randomised controlled trials (RCTs) designed to assess the effectiveness of single or multiple interventions for prevention of aspiration pneumonia will be included in the review. Articles must include aspiration pneumonia as primary outcome, as well as sufficient information on study design, characteristics of participants and interventions provided to be eligible. Studies of postoperative aspiration pneumonia will be excluded.

Condition or domain being studied

Single and multiple interventions for prevention of aspiration pneumonia. Eligible studies must refer radiological confirmation of pneumonia or any recognised diagnostic criteria.

Participants/population

Patients aged 65 and older who were at risk for aspiration pneumonia. This will be based on documented oropharyngeal dysphagia, previous stroke, previous aspiration, or tube feeding.

Intervention(s), exposure(s)

All original RCTs that study the effectiveness of single or multiple prevention programs for aspiration pneumonia will be included.

Comparator(s)/control

Interventions must include a comparison with placebo, no intervention (usual care), or another type of intervention.

Context

Contexts to be considered include hospitals; rehabilitation centres; nursing homes and geriatric long term care facilities.

Main outcome(s)

The main outcome is the incidence of pneumonia within the trial period. Pneumonia must be diagnosed using chest radiography or any recognised clinical criteria.

Timing and effect measures

Included studies must report the incidence of pneumonia from baseline until the final follow-up. Data analysis

of such studies must include valid statistical methods that enable comparisons between groups.

Additional outcome(s)

Secondary outcomes will address the incidence of aspiration, mortality, changes in body weight and functional outcome according to a standardised scale during the intervention period. All adverse effects resulting from such interventions will be analysed.

Timing and effect measures

Included studies must report secondary outcomes and adverse effects observed from baseline until the final follow-up. Data analysis of such studies must include valid statistical methods that enable comparisons between groups.

Data extraction (selection and coding)

Two reviewers (JS and MM) will independently perform the initial selection of studies based on title and abstract. Full-text of the articles obtained in the initial phase will be analysed by the same reviewers, who will independently select eligible articles for inclusion in the review. Disagreement will be resolved through discussion and consensus with two additional reviewers (LJ and OR). The process of study selection will be documented in a flow chart, as recommended by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009). After the selection phase, one reviewer (JS) will extract data on study design, demographics, intervention, study validity and effect measurement from all included articles. The extracted data will be checked by three researchers (MM, LJ and OR). The reviewers will contact the authors in case of missing data or additional details. An Excel spreadsheet will be created for the registry of the search strategy and its results, as well as to record the decisions made in each selection phase and the data extracted. Reference: Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Journal of Clinical Epidemiology 2009;62(10):1006–12.

Risk of bias (quality) assessment

Study validity will be independently assessed by two reviewers (JS and MM) according to The Cochrane Collaboration's tool for assessing risk of bias (Higgins et al., 2011). Adequate follow-up will be considered if 80% or more of the participants are still in the sample at the end of the study. Reference: Higgins Julian P T, Altman Douglas G, Gøtzsche Peter C, Jüni Peter, Moher David, Oxman Andrew D et al. The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials BMJ 2011; 343: d5928

Strategy for data synthesis

Due to the expected heterogeneity between interventions, data analysis will be qualitative. Thus, interventions will be classified as having positive, negative or no overall effect on the primary outcome depending on whether a significant difference in AP between groups is demonstrated. Data synthesis will be organised in a Summary of Findings table as recommended in Chapter 11 of the Cochrane Handbook for Systematic Reviews of Interventions, including information on participant demographics, methodological quality and intervention methods and effect (Schünemann et al., 2011). Reference: Schünemann HJ, Oxman AD, Higgins JPT, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and ‘Summary of findings' tables. In: Higgins JPT, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from www.handbook.cochrane.org.

Analysis of subgroups or subsets

The results for each trial will be grouped by intervention category (dietary interventions and compensatory strategy, pharmacologic therapies, oral hygiene, feeding tube and training and education) and, if the necessary data are available, by pathology (e.g. stroke, dementia).

Contact details for further information

Joana Santos
santosjoana@ua.pt

Organisational affiliation of the review

School of Health, University of Aveiro (ESSUA)
https://www.ua.pt/essua/#

Review team members and their organisational affiliations

Ms Joana Santos. University of Aveiro
Professor Óscar Ribeiro. University of Aveiro, Department of Education and Psychology (DEP), and CINTESIS – Center for Health Technology and Services Research (CINTESIS.UA), Portugal.
Professor Luis Jesus. University of Aveiro, School of Health (ESSUA), and Institute of Electronics and Informatics Engineering of Aveiro (IEETA), Portugal.
Professor Maria Matos. University of Aveiro, School of Health (ESSUA), Portugal

Type and method of review

Prevention, Systematic review

Anticipated or actual start date

01 July 2019

Anticipated completion date

01 October 2019

Funding sources/sponsors

None

Conflicts of interest

Language

English

Country

Portugal

Stage of review

Review Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

Humans; Pneumonia, Aspiration; Risk Factors

Date of registration in PROSPERO

30 September 2019

Date of publication of this version

30 September 2019

Details of any existing review of the same topic by the same authors

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	Yes	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Versions

30 September 2019