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## **Interventions to Prevent Non-Critical Care Hospital Acquired Pneumonia – a Systematic Review**

## **ABSTRACT**

### **Background**

Hospital Acquired Pneumonia is a significant burden to healthcare systems around the world. Although there is a considerable body of evidence on prevention of Ventilator Associated Pneumonia, less is known about strategies to prevent hospital-acquired pneumonia in non-critical care settings.

### **Objective**

To systematically review the Randomised Controlled Trial evidence for prevention of hospital-acquired pneumonia in non-critical care settings.

### **Methods**

We searched EMBASE, CINAHL+, MEDLINE and the Cochrane Library. Seventeen different searches were conducted in parallel through each database. Studies were included if they were randomised controlled trials reporting hospital-acquired pneumonia as an endpoint. Studies were excluded if they were performed in critical care or community settings. All studies published up to **the end of December 2014** were considered, with no language restrictions. Data were independently extracted by two authors and the Delphi risk of bias tool was applied to assess trial quality.

### **Results**

**5101** titles were identified across 17 searches. Only 2 studies were eligible for inclusion in the final review, one from a search of physical therapy interventions and one from a search of enteral feeding. The heterogeneity of the interventions did not permit meta-analysis. One

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trial suggested possible benefits to early mobilisation; the other trial suggested no benefit or harm from early enteral feeding via nasogastric tube. Both trials enrolled patients with acute stroke. No trials in non-stroke, non-critical care populations were eligible for inclusion in the review.

## **Conclusions**

There is currently insufficient trial evidence on preventing non-critical care hospital-acquired pneumonia to make recommendations on practice.

## **INTRODUCTION**

Hospital Acquired Pneumonia (HAP) is a major source of morbidity and mortality[1-6]. Whilst considerable effort has been made to study and prevent ventilator-acquired pneumonia (VAP)[7], much less is known about hospital-acquired pneumonia outside critical care facilities. The estimated prevalence of non-critical care HAP is uncertain; estimates vary between 1% and 8% of hospital admissions depending on the subgroup of patients studied, with older people being at particular risk. HAP is associated with a mortality rate of up to 70% either as a direct consequence or contributing to other factors. It typically adds 7-9 days onto a hospital admission[8], and hence carries significant financial burden.

The aetiopathogenesis of HAP is thought to be an interaction between microaspiration or macroaspiration of oral flora, impaired defence mechanisms (for example impaired cough reflexes, reduced mucociliary escalator activity, impaired pulmonary immunity) and, at least for some patient populations, changes to oral flora as a result of residence in hospital and exposure to antimicrobial agents[9]. Treatment of hospital acquired pneumonia requires additional antimicrobial therapy, may involve treatment of resistant organisms, and each episode of infection is likely to produce deleterious effects on physical function, cardiovascular events, delirium, nutrition and psychological status. It is thus important to find ways to prevent hospital acquired pneumonia outside the critical care environment.

Although interventions to prevent VAP have been well studied, and several effective interventions are known[7], interventions to prevent hospital acquired pneumonia outside critical care units are much less studied, and to date, no systematic review has synthesised the trial evidence in non-critical care settings. In this paper, we report the results of a systematic

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review of interventions to prevent non-critical care HAP as a starting point for future development of interventions to prevent this condition.

## **METHODS**

### **Scope of review**

Following a preliminary literature search, an expert panel consisting of the authors was convened, with representation from geriatric medicine, infectious diseases and microbiology. Candidate interventions were identified and discussed based on observational data, use in critical care settings, biological plausibility and topical interest. A range of pharmacological and non-pharmacological interventions were identified for review, and the review was conducted according to a prespecified protocol based on the PRISMA guidelines[10].

### **Inclusion & Exclusion criteria**

The systematic review sought to include only randomised controlled trials of interventions to reduce HAP in the non critical care setting. Studies comparing intervention with either placebo or usual care, or comparing two different interventions were included in the analysis. Both parallel group and crossover studies were eligible for inclusion. Studies examining community-acquired pneumonia or pneumonia acquired in non-hospital healthcare facilities (e.g. nursing homes) were excluded, as were those which examined VAP.

### **Data sources and search strategies**

MEDLINE, CINAHL+ and EMBASE databases were searched; search results up to **December 31<sup>st</sup> 2014** were included. The Cochrane library was also checked for original research and systematic reviews on HAP. References of included papers were hand searched to identify other papers of interest. No language restrictions were applied to the searches. The search strategies used are included in Appendix A.

## **Interventions**

17 interventions were examined in three different groups: Group A ‘Patient based Interventions’ such as risk assessment and mouthwash; Group B ‘Medications’ including sedatives, anti-emetics and pro-kinetics; and Group C ‘Staff Interventions & Environmental Factors’ including handwashing, staff education and deep cleaning. The full search strategy is attached in Appendix A.

## **Outcomes**

The primary outcome we sought to extract was the incidence of HAP. Secondary outcome measures were mortality, length of stay, use of multiple antibiotics and total number of days of antibiotic therapy. Data were also extracted on age, sex, description of intervention, comorbid disease, medication use and a description of the healthcare setting.

## **Data extraction and quality assessment**

Standardised proformas for data extraction and quality assessment were used. Selection of abstracts and full papers for retrieval was performed by two authors (SMcA and MDW) with differences in selection resolved by consensus. Data from included papers were extracted independently by two authors (SMcA and MDW), with differences resolved by consensus. Risk of bias assessment was performed using categories from the Delphi risk of bias tool[11].

## **Data synthesis**

For each of the 17 searches, we aimed to combine incidence data from similar studies by meta-analysis via Peto odds ratios using random-effects modelling. Where studies were too dissimilar to perform meta-analysis we aimed to provide narrative synthesis of the study results.



## **RESULTS**

A total of 5101 titles were identified by the 17 searches. Figures for flow through the study searches are given in Table 1. Only two studies[12,13] satisfied the criteria for inclusion; one from search 2 (early mobilisation & rehabilitation) and one from search 5 (enteral feeding). Meta-analysis of the data from these studies was therefore not possible. A summary description of both studies is given in Table 2.

### **Quality assessment**

Both trials included in this review were open trials. The randomisation process is well described in the FOOD trial[12], albeit with a slight procedural change between the pilot and the main phase. The Turn-Mob trial[13] stated that randomisation took place but without describing the process. All patients were followed up with intention to treat and all patients were accounted for in both trials. Pneumonia was one of many secondary outcomes measured in the FOOD trial and the criteria used to make the diagnosis are unclear. In both trials there is potential for confounding, such as the degree of involvement by relatives in Turn-Mob programme, or patients switching between tube and oral feeding in the FOOD trial.

### **Study results – the TurnMob trial**

Turn-Mob was a randomised trial conducted across two university hospitals in Mexico City from March 2006 to January 2007. 225 patients presenting with acute ischaemic stroke were enrolled. Patients were randomized to standard care alone or manual turning and passive mobilisation plus standard care. Standard care comprised oxygen, adequate nutrition and hydration, anti-platelet agents, glycaemic control, routine measurements and ‘general nursing care’ which included the nurses changing the position of the patients three times per day. In

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addition to this, the intervention group received regular changes in position (every two hours) and passive mobilisation of the limbs (every six hours) from a relative trained in the procedure by a rehabilitation physician.

Of the 223 patients randomised, 48 developed HAP. There was a lower proportion with HAP in the intervention group (Table 2). Recalculation of the relative risk from data supplied in the trial report shows a relative risk of HAP of 0.47. All patients were followed up for 2 weeks after discharge with no further cases identified.

### **Study results – the FOOD trial**

The second FOOD trial, included in this review, investigated early feeding in dysphagic patients compared with no feeding for at least 7 days after randomisation. Patients in the intervention group could receive nutrition by nasogastric (NG) tube or by percutaneous endoscopic gastrostomy (PEG) feeding. A total of 859 patients were recruited, of which 149 were co-enrolled into more than one trial in the FOOD trial programme.

The early intervention group had similar rates of pneumonia to the control group; case fatality rates for HAP were similar in both arms (intervention group 77/132, 58%; control group 74/133, 56%). Overall fatality rates were lower in the intervention group (182/429; 42%) when compared to the control group (207/430; 48%).

## **DISCUSSION**

No eligible trials of pharmacological interventions to prevent non-critical care HAP were identified by the search strategy. There was some evidence from the Turn-Mob programme

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that early mobilisation may be beneficial in select patients; results from the FOOD trial showed no evidence of either benefit or harm from early enteral feeding via nasogastric tube.

Both trials were conducted in patients admitted with acute stroke. Such patients are known to be at high risk of aspiration, as swallowing dysfunction is very common in the first few days after an acute stroke[14]. It is questionable however whether these results are generalizable to the wider group of older hospitalised patients; although some of this wider group will be at risk of microaspiration even in the absence of overt dysphagia[15]; the mix of comorbidity, immune impairment and antibiotic exposure (all risk factors for HAP) may differ between patients with and without acute stroke.

The application of the TurnMob programme depended on significant input from family members, in a healthcare system with significant differences to that in some developed countries. It is therefore not clear whether such a programme would be deliverable in other healthcare systems, or whether the benefits in other countries would be replicated.

The lack of **randomised controlled trial** evidence that our search uncovered is striking; despite a wide search strategy encompassing multiple areas of intervention. Although healthcare acquired infections have been a key focus of infection control policy in recent years, much of the effort has focussed on Meticillin resistant *Staphylococcus aureus* (MRSA) infection and on *Clostridium difficile* associated diarrhoea. However, pneumonia is a common, expensive and dangerous healthcare acquired infection, and is beginning to garner more attention[16]. The evidence base for prevention lags far behind this rising level of interest.

A number of non-randomised studies have been published recently, which may provide the foundation for future well-designed RCTs. Introduction of a care bundle to enhance early mobility[17] was associated with a lower risk of HAP (OR 0.39; 95% CI 0.22 to 0.68,  $p=0.001$ ), although falls rates were non-significantly higher in the early mobility group. Introduction of a basic nursing oral care package led to a 40% reduction in the occurrence of HAP compared to historical controls[18]; similar results were seen in a small study of neurologically impaired patients[19]. In a stroke population, the introduction of dysphagia screening was associated with a lower rate of HAP compared to historical controls (OR 0.43; 95%CI 0.26 to 0.71;  $p=0.001$ )[20]. Such studies, in conjunction with the existing evidence base in ventilated patients, help to build the case for future trials.

### **Strengths and Weaknesses**

The application of systematic review methodology, using prespecified criteria and focussing only on randomised controlled trials all contribute to the rigour of this review. We searched for a wide range of interventions, which enhances the utility of the review, and reinforces the lack of research in this area. The use of multiple databases, handsearching of references and inclusion of non-English language papers increases the likelihood that we have captured all relevant studies, although there may of course be studies that we have missed (perhaps as a result of examining a wide range of interventions), or which remain unpublished.

The dearth of studies retrieved by this review limits the conclusions that can be drawn (beyond illustrating the paucity of intervention research in this area), but should not be viewed as a methodological weakness. The inclusion of observational studies would give additional information, albeit subject to the constraints of bias and confounding; a review of this additional literature lies outwith the boundaries of the current work however. A further

weakness is the lack of detailed phenotypic information about both the trial populations and the co-interventions that they were subject to. In particular, no information was retrievable on the type of pathogens causing pneumonia, on the vaccination status of the participants (for either influenza or pneumococcus), or on the immunocompetence of the individuals studied. Such information may be of considerable importance in targeting and assessing treatment strategies, and future trials should collect as many of these variables as possible.

### **Recommendations for practice and future research**

Insufficient evidence currently exists to make any recommendation as to how best to prevent hospital acquired pneumonia in non-critical care settings. Given this lack of evidence, the severe nature of this common condition, studies examining the effect of interventions to prevent HAP are clearly required. It is important that such studies target older people (i.e. those who are most at risk) and that such studies target a wide range of hospitalised older people, not just on a condition-specific basis such as stroke.

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## **Appendix A Search Strategies**

### **Part A – Patient Interventions**

Search 1:

“Pneumonia” AND [“Cross infection” OR “Hospital Acquired” OR “Health Care Associated” OR “Nosocomial”] AND [“Risk Assessment” OR “Scoring Tool” OR “Scoring System” OR “Diagnostic Tool”]

Search 2:

“Pneumonia” AND [“Cross infection” OR “Hospital Acquired” OR “Health Care Associated” OR “Nosocomial”] AND [“Early Mobilisation” OR “Rehabilitation”]

Search 3:

“Pneumonia” AND [“Cross infection” OR “Hospital Acquired” OR “Health Care Associated” OR “Nosocomial”] AND [“Dental Care” OR “Oral Hygiene” OR “Mouthwash” OR “Sanguinaria” OR “Chlorhexidine” OR “Benzethonium” OR “Benzalkonium”]

Search 4:

“Pneumonia” AND [“Cross infection” OR “Hospital Acquired” OR “Health Care Associated” OR “Nosocomial”] AND “Spirometry”

Search 5:

“Pneumonia” AND [“Cross infection” OR “Hospital Acquired” OR “Health Care Associated” OR “Nosocomial”] AND [“Intubation, Gastrointestinal” OR “NG Tube” OR “Nasogastric Tube” OR “NJ Tube” OR “Nasojejunal Tube” OR “Enteral Nutrition” OR “Enteral Feeding”]

### **Part B – Medications**

Search 6:

“Pneumonia” AND [“Cross infection” OR “Hospital Acquired” OR “Health Care Associated” OR “Nosocomial”] AND [“Anti-Ulcer” OR “Antacids” OR “Aluminium Hydroxide” OR “Magnesium Carbonate” OR “Magnesium Trisilicate” OR “Hydrotalcite” OR “Acidex” OR “Gaviscon” OR “Peptac” OR “Histamine H2 Antagonists” OR “Histamine H2-receptor Antagonists” OR “Cimetidine” OR “Famotidine” OR “Nizatidine” OR “Ranitidine” OR “Proton Pump Inhibitors” OR “Esomeprazole” OR “Lansoprazole” OR “Omeprazole” OR “Pantoprazole” OR “Rabeprazole” OR “Tripotassium Dicitratobismuthate” OR “Sucralfate” OR “Prostaglandins E, Synthetic” OR “Misoprostol”]

Search 7:

“Pneumonia” AND [“Cross infection” OR “Hospital Acquired” OR “Health Care Associated” OR “Nosocomial”] AND [“Hypnotics” OR “Sedatives” OR “Anxiolytics” OR “Anti-Anxiety Agents” OR “Benzodiazepines” OR “Barbiturates” OR “Antipsychotic drugs” OR “Diazepam” OR “Alprazolam” OR “Chlordiazepoxide” OR “Lorazepam” OR “Oxazepam” OR “Buspirone” OR “Meprobamate” OR “Benperidol” OR “Chlorpromazine”]

OR “Flupentixol” OR “Flupenthixol” OR “Haloperidol” OR “Levomepromazine” OR “Methotrimeprazine” OR “Pericyazine” OR “Periciazine” OR “Perphenazine” OR “Pimozide” OR “Promazine” OR “Sulpiride” OR “Trifluoperazine” OR “Zuclopenthixol” OR “Amisulpride” OR “Aripiprazole” OR “Clozapine” OR “Olanzapine” OR “Paliperidone” OR “Quetiapine” OR “Risperidone” OR “Pipotiazine” OR “Pipothiazine” OR “Amobarbital” OR “Phenobarbital” OR “Butobarbital” OR “Secobarbital”]

Search 8:

“Pneumonia” AND [“Cross infection” OR “Hospital Acquired” OR “Health Care Associated” OR “Nosocomial”] AND [“Angiotensin-Converting Enzyme Inhibitors” OR “ACE inhibitors” OR “Captopril” OR “Cilazapril” OR “Enalapril” OR “Fosinopril” OR “Imidapril” OR “Lisinopril” OR “Moexipril” OR “Perindopril” OR “Quinapril” OR “Ramipril” OR “Trandolapril”]

Search 9:

“Pneumonia” AND [“Cross infection” OR “Hospital Acquired” OR “Health Care Associated” OR “Nosocomial”] AND [“Antibiotic Policy” OR “Antibiotic Stewardship” OR “Antibiotic Restriction”]

Search 10:

“Pneumonia” AND [“Cross infection” OR “Hospital Acquired” OR “Health Care Associated” OR “Nosocomial”] AND [“Vaccination” OR “Influenza Vaccines” OR “Pneumococcal Vaccines” OR “Bacterial Vaccines” OR “Mass Vaccination” OR “Parainfluenza Vaccines” OR “Pseudomonas Vaccines” OR “Staphylococcal Vaccines” OR “Vaccines, Attenuated” OR “Vaccines, Conjugate” OR “Vaccines, Acellular” OR “Tuberculosis Vaccines”]

Search 11:

“Pneumonia” AND [“Cross infection” OR “Hospital Acquired” OR “Health Care Associated” OR “Nosocomial”] AND [“Prokinetic” OR “Gastrokinetic” OR “Gastroprokinetic” OR “Metoclopramide” OR “Domperidone” OR “Erythromycin” OR “Mitemincinal” OR “Benzamides” OR “Cisapride” OR “Mosapride” OR “Itopride” OR “Prucalopride” OR “Renzapride” OR “Tegaserod”]

### **Part C– Staff interventions& Environmental Factors**

Search 12:

“Pneumonia” AND [“Cross infection” OR “Hospital Acquired” OR “Health Care Associated” OR “Nosocomial”] AND [“Hand Washing” OR “Hand Hygiene”]

Search 13:

“Pneumonia” AND [“Cross infection” OR “Hospital Acquired” OR “Health Care Associated” OR “Nosocomial”] AND [“Alcohol Gel” OR “Hand Gel”]

Search 14:

“Pneumonia” AND [“Cross infection” OR “Hospital Acquired” OR “Health Care Associated” OR “Nosocomial”] AND [“Infection Control” OR “Barrier Nursing” OR “Reverse Barrier Nursing” OR “Patient Isolation”]

Search 15:

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“Pneumonia” AND [“Cross infection” OR “Hospital Acquired” OR “Health Care Associated” OR “Nosocomial”] AND [“Education" OR "Staff Development” OR "Education, Nursing, Continuing" OR "Education, Medical, Continuing" OR "Education, Continuing"OR "Education, Medical"]

Search 16:

“Pneumonia” AND [“Cross infection” OR “Hospital Acquired” OR “Health Care Associated” OR “Nosocomial”] AND [“Gloves” OR “Masks” OR “Gowns” OR “Personal Protective Equipment” OR “Personal Protection Equipment”]

Search 17:

“Pneumonia” AND [“Cross infection” OR “Hospital Acquired” OR “Health Care Associated” OR “Nosocomial”] AND [“Deep Cleaning” OR “Environmental Cleaning”]

**Table 1. Search flowcharts**

	Risk Assessment	Early Mobilisation & Rehabilitation	Oral Hygiene	Spirometry	Enteral Feeding	Acid Suppressant Medication	Hypnotics & Sedatives	ACE inhibitors	Antibiotic Stewardship	Vaccinations	Prokinetic Medication	Hand Washing	Alcohol Gel	Barrier Nursing	Education Programmes	Personal Protective Equipment	Environmental Cleaning
Titles identified	706	61	325	16	291	343	73	7	67	220	507	298	4	1713	394	66	10
Abstracts retrieved	102	4	63	8	46	63	7	2	2	17	4	21	2	193	55	11	6
Full papers retrieved	9	2	10	2	24	27	3	2	1	1	0	2	0	3	0	0	1
Studies included	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0

**Table 2. Characteristics of included studies**

Title	n	Mean Age	% male	Study population	Intervention	Comparator	Length of follow up	Intervention group incidence	Comparator group incidence	Relative risk
Turn Mob(13)	223	73	46	Stroke	Additional passive mobilisation	Standard Care	To discharge with follow up phone call at 14 days	14/111 (13%)	30/112 (27%)	0.47
FOOD(12)	859	76	46	Stroke	Early Enteral tube feeding	Avoid tube feeding for at least 7 days	To discharge with follow up questionnaire 6 mths post randomisation	132/429 (31%)	133/430 (31%)	0.99

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