

Antibiotic Use and Associated Factors in Patients with Dementia: A Systematic Review

Tessa van der Maaden · Simone A. Hendriks · Henrica C. W. de Vet ·
Menno T. Zomerhuis · Martin Smalbrugge · Elise P. Jansma · Raymond T. C. M. Koopmans ·
Cees M. P. M. Hertogh · Jenny T. van der Steen

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Abstract

Background Infections frequently occur in patients with dementia and antibiotics are often prescribed, but may also be withheld.

Objectives The aim of this systematic review is to provide a systematic overview of the prevalence of antibiotic use, and factors associated with prescribing antibiotics in patients with dementia.

Data Sources A systematic search of MEDLINE, EMBASE, PSYCINFO, CINAHL, and the Cochrane library

databases until February 13, 2014 was performed, using both controlled terms and free-text terms.

Results Thirty-seven articles were included. The point prevalence of antibiotic use in patients with dementia ranged from 3.3 to 16.6 %. The period prevalence ranged from 4.4 to 88 % overall, and from 23.5 to 94 % in variable time frames before death; the median use was 52 % (median period 14 days) and 48 % (median period 22 days), respectively. Most patients with lower respiratory tract infections or urinary tract infections (77–91 %) received antibiotic treatment. Factors associated with antibiotic use related to patients, families, physicians, and the healthcare context. More severe dementia and a poor prognosis were associated with less antibiotic use in

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T. van der Maaden · S. A. Hendriks · H.
C. W. de Vet · M. Smalbrugge · C. M. P. M. Hertogh ·
J. T. van der Steen
EMGO Institute for Health and Care Research, VU University
Medical Center, Van der Boechorststraat 7,
1081 BT Amsterdam, The Netherlands
e-mail: t.vandermaaden@vumc.nl

S. A. Hendriks
e-mail: s.hendriks@vumc.nl

H. C. W. de Vet
e-mail: hcw.devet@vumc.nl

M. Smalbrugge
e-mail: m.smalbrugge@vumc.nl

C. M. P. M. Hertogh
e-mail: cmpm.hertogh@vumc.nl

T. van der Maaden · S. A. Hendriks · M. Smalbrugge ·
C. M. P. M. Hertogh · J. T. van der Steen (✉)
Department of General Practice & Elderly Care Medicine,
VU University Medical Center, Van der Boechorststraat 7,
1081 BT Amsterdam, The Netherlands
e-mail: j.vandersteen@vumc.nl

H. C. W. de Vet
Department of Epidemiology and Biostatistics, VU University
Medical Center, Van der Boechorststraat 7,
1081 BT Amsterdam, The Netherlands

M. T. Zomerhuis
Pniël, Lelie Zorggroep, Center for Specialized Geriatric Care,
Oudedijk 15, 3062 AB Rotterdam, The Netherlands
e-mail: m.zomerhuis@leliezorggroep.nl

E. P. Jansma
Medical Library, VU University Amsterdam,
De Boelelaan 1105, 1081 HV Amsterdam, The Netherlands
e-mail: i.jansma@vu.nl

R. T. C. M. Koopmans
Department of Primary and Community Care, Radboud
University Medical Centre, Nijmegen 117 ELG, Postbus 9101,
6500 HB Nijmegen, The Netherlands
e-mail: raymond.koopmans@radboudumc.nl

R. T. C. M. Koopmans
Joachim en Anna, Center for Specialized Geriatric Care,
Groesbeekseweg 327, 6523 PA Nijmegen, The Netherlands

various countries. Associations with aspiration and illness severity differed by country.

Conclusions and Implications Antibiotic use in patients with dementia is substantial, and probably highly associated with the particular healthcare context. Future studies may report antibiotic use by infection type and stage of dementia, and compare cross-nationally.

Key Points

The prevalence of antibiotic use for patients with dementia is substantial, varies between countries, and depends on the particular healthcare setting

More severe dementia and a poor prognosis were related to fewer antibiotics in patients with dementia in various countries

Future studies investigating antibiotic prescription patterns should report antibiotic use by type of infection, stage of dementia, and goals of antibiotic treatment in multiple settings

1 Introduction

In 2010, 35.6 million people were estimated to have dementia worldwide and this number is expected to nearly double every 20 years [1]. Dementia patients are susceptible to infections, including respiratory tract infections (RTIs), urinary tract infections (UTIs), and skin and soft tissue infections [2, 3], and decision makers such as physicians, patients, and families are often faced with complex treatment decisions, especially at the end of life.

Treatment decisions about antibiotics, specifically in patients with dementia, imply ethical considerations such as whether to accept potential burden caused by treatment, and weighing best interests against patient and family preferences [4, 5]. Furthermore, patients with dementia may be unable to express symptoms and complaints, and typical symptoms of the infection are often absent [6, 7]. Long-term care environments may involve specific challenges such as the absence of diagnostic resources, which complicates appropriate antibiotic treatment [8, 9]. These challenges in the treatment of infections for patients with dementia may lead to variability in antibiotic use. Eventually this can result in burdensome side effects and the development of antibiotic-resistant microbes, which pose a major health risk, especially in older and institutionalized populations [10, 11].

Studies that report on withholding treatment in advanced stages of dementia often focus on cardiopulmonary resuscitation (CPR), artificial nutrition or hospitalization [12–14], which suggests that antibiotic use is frequently regarded as a routine treatment. In addition, patients, families, and professionals often do not realize that dementia is a life-limiting disease, which may result in the deployment of potentially burdensome medical interventions in dementia including intravenous antibiotics and fluids [15–18]. Antibiotic use in dementia may vary across different countries and settings [19, 20]. However, an overview of the actual proportion of patients with dementia that receive antibiotic treatment worldwide in different settings and for various indications is lacking, as is a mapping of the factors associated with its use.

The objectives of this review are to provide a comprehensive overview of (i) the prevalence of antibiotic use in patients with dementia in general and for specific infections, and of (ii) factors associated with antibiotic treatment or withholding treatment in dementia, in various care settings and countries.

2 Methods

2.1 Literature Search

We performed systematic searches in the bibliographic databases PubMed, EMBASE.com, PsycINFO (via EBSCO) and The Cochrane Library (via Wiley) from inception to February 13, 2014. Search terms included controlled terms from MeSH in PubMed, EMtree in EMBASE.com and thesaurus terms in PsycINFO as well as free-text terms. We used free-text terms only in The Cochrane Library. Search terms expressing ‘dementia’ were used in combination with search terms comprising ‘antibiotics’ (see electronic supplementary material [ESM], online resource A). The references of the identified articles were searched for other relevant publications.

2.2 Inclusion Criteria

Articles were included if they reported about antibiotic use in patients with dementia. We excluded articles if they were (i) not reporting about people with dementia or not referring to a population of which at least 50 % had dementia; (ii) not containing empirical data such as in reviews, editorials, letters, and legal cases; (iii) case reports or $n = 1$ studies; (iv) not reporting about prevalence of antibiotic use or about factors associated with antibiotic use; (v) written in languages other than English, Dutch, French or German.

2.3 Selection Process

Two reviewers (TM and EPJ) independently screened all potentially relevant titles and abstracts for eligibility. If possibly eligible, the full-text article was retrieved and evaluated. Differences in judgment were resolved through a consensus procedure. Data extraction was performed in duplicate by TM and three extra reviewers (SH, MZ, JTS), independently. We resolved any discrepancies in data extracted by discussion until consensus was reached. Data were extracted using a pilot-tested form that included design of the study, subject characteristics, setting, type of infection, diagnosis of the infection, severity of the dementia, prevalence of antibiotic use, and any factors associated with antibiotic use. When the same data about antibiotic prevalence were published in multiple publications, we used the data from the publication that matched our research question best, or, if indifferent, the first publication that reported on the largest possible appropriate selection of participants. We abstracted any factor that was examined for an association with antibiotic use, regardless of country and setting. We therefore abstracted all factors and subsequently categorized by content.

2.4 Assessment of Methodological Quality and Usefulness

The methodological quality of the included articles was assessed using the Mixed Methods Appraisal Tool (MMAT) [21], which enabled the appraisal of both quantitative and qualitative studies within their methodological domain resulting in comparable quality ratings. The quality ratings range from 0 %, when none of four criteria are met, to 100 % when all criteria are met.

In addition to the MMAT scoring, we developed and applied more specific criteria to rate the usefulness of included articles for the purpose of our review, and rated these as useful, somewhat useful or not useful (for further explanation see ESM, online resource B). The MMAT scores and the usefulness of articles were assessed in duplicate and independently by TM and the three extra reviewers (SH, MZ, JTS) and disagreements were resolved by discussion. Articles that scored ≤ 25 % on the MMAT were excluded when evaluated as somewhat useful; articles evaluated as not useful were excluded regardless of the MMAT score.

3 Results

The literature search generated a total of 1,867 references: 892 from PubMed, 843 from EMBASE.com, 114 from PsycINFO, 18 from the Cochrane Library, and an

additional 10 references from reference lists. After removing duplicates, 1,556 references remained. After screening titles and abstracts of references retrieved, 49 articles fulfilled the eligibility criteria, and quality and usefulness was adequate for 37 articles (Fig. 1). Five studies were reported in more than one article, and we therefore report data from a total of 34 studies. We found 14 articles reporting about the prevalence of antibiotic use, overall or per infection, 13 articles examining the association of one or more factors with antibiotic use, and 10 articles that reported about both prevalence of antibiotic use and associated factors (Fig. 1).

3.1 Prevalence of Antibiotic Use

Of the 24 articles that reported prevalence of antibiotic use (see ESM, online resource C), most (17) referred to nursing homes, long-term care facilities (LTCFs) or similar settings, and a few referred to a hospital setting (6), or home situation (1). Articles assessed the point prevalence of antibiotic use (3), period prevalence (7), antibiotic use in the last period before death (6) or antibiotic use during a specific infectious episode (8).

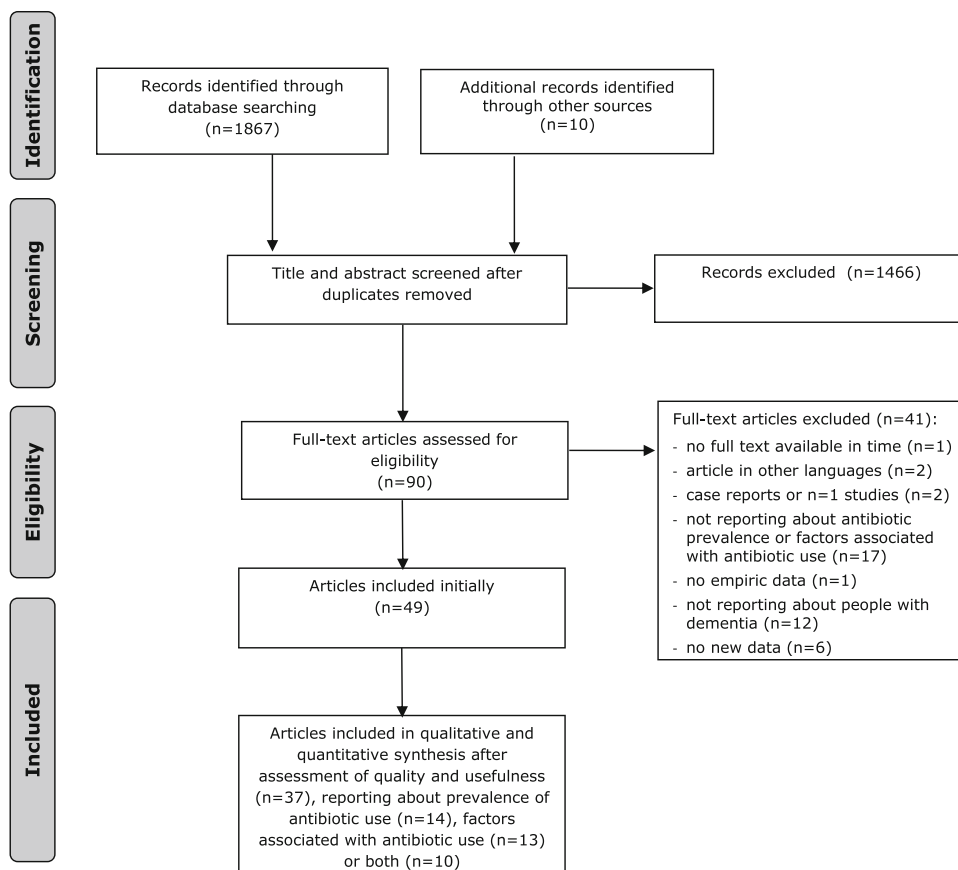
In nursing homes in Finland, Italy, and Canada, the point prevalence of antibiotic use ranged between 3.3 and 16.6 % [19, 22, 23]. The point prevalence depended on the setting; in an Italian study, it was 3.3 % in nursing homes, and 15.2 % in community-dwelling patients (Fig. 2a and ESM, online resource C) [19].

The period prevalence of patients who received at least one course of antibiotics in a nursing-home setting was 4.4 % in 3 days in a selection of European countries and Israel [24], and 88 % in a time span of 6 months in the US (Fig. 2b and ESM, online resource C) [25]. The remaining five studies were conducted in hospitals in France, Israel, Canada, and the US, and antibiotic use ranged from 21.8 % during the first 14 days of admission, to 86.2 % during the stay in a hospital with a mean length of stay of 3.6 days. The median period prevalence in these articles was 52 % for a median period of 14 days [26–30].

The six articles that examined period prevalence of antibiotic use until death found percentages that ranged from 23.5 % receiving antibiotics in the last 2 days of life at home in Japan [31], to 94 % during terminal hospitalization in the US [32]. The four remaining studies were conducted in Italian and US nursing homes or hospice agencies and antibiotic use was assessed in the last 6 months, 30 days or 14 days of life, and the last 7 days in hospice care, with a median prevalence of 48 % for a median period of 22 days (Fig. 2c and ESM, online resource C) [28–30, 33–36].

Five articles reported about treatment for patients with lower respiratory infections (LRIs) or pneumonia, mostly

Fig. 1 Flowchart of the search and selection procedure of studies



diagnosed by clinical criteria (Fig. 2d and ESM, online resource C). Three US articles reported that 85.3–91.1 % of patients received antibiotic therapy [37–39], and two Dutch articles reported percentages of 77 and 79 % [40, 41].

Antibiotic treatment of UTIs was provided in 77.9 % of episodes in US nursing homes [6]. An article that focused on treatment of feverish conditions reported that antibiotics were used in 37.8 % of 172 feverish episodes in 104 patients in the US, of which 93 episodes were RTIs, 67 were UTIs, and 25 were systemic infections; all diagnoses were based on physical examinations [42]. Another article reported that 43.1 % of 102 feverish episodes in 193 patients were treated with antibiotics in Finland [43].

3.2 Factors Associated with Antibiotic Use

Papers reported a total of 57 factors that were associated with antibiotic use and could be categorized into factors that related to (i) the patient's health status, (ii) persons involved in the decision making such as patients, physicians or families, and (iii) the healthcare context, such as country and setting (Tables 1, 2, 3). For only three articles, the search for factors associated with antibiotic use was the

primary goal, and these articles investigated associations of multiple factors with antibiotic use for pneumonia in patients with dementia [37, 41, 44]. Most articles tested one or a few factors that were or were not based on specific hypotheses.

3.2.1 Patient's Health Status

The majority of factors associated with antibiotic use in the included articles related to the patient's health status (27/57); four factors were reported in two or more articles, and showed consistent associations with fewer antibiotic treatments (Table 1—highlighted rows). The severity of dementia was studied in four articles and all found that patients with more severe dementia were less likely to receive antibiotics [33, 39, 41, 44]. Furthermore, a poor prognosis was associated with fewer antibiotics in a selection of European nursing homes [24], and in a Dutch study which assessed physicians' subjective predictions in a survey [45]. The latter reported that three-quarters of the physicians would consider a mortality risk of 75–90 % in spite of treatment sufficiently high to justify withholding antibiotics [45]. Lastly, illness severity and eating dependence, both pre-LRI and at the time of the treatment

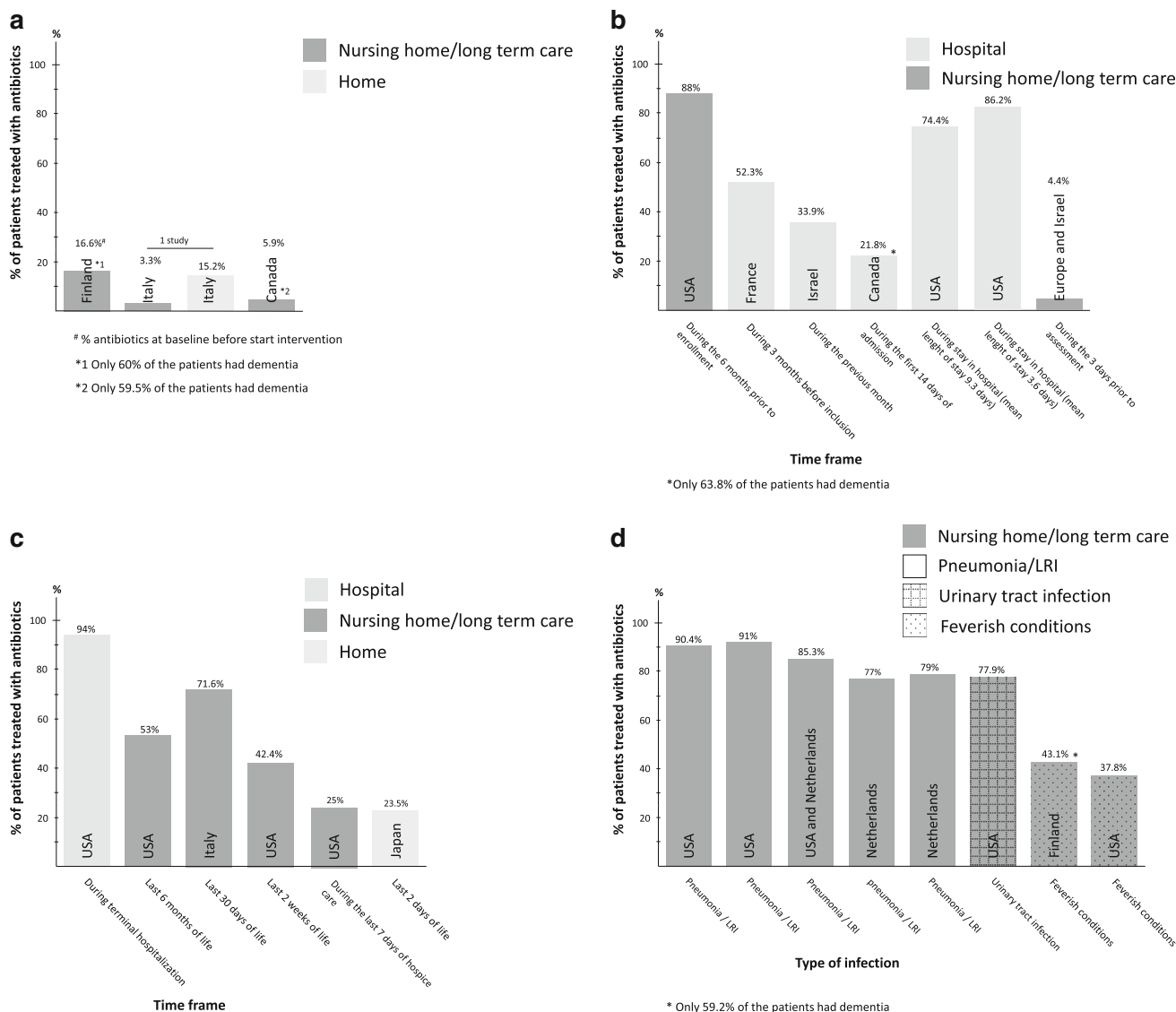


Fig. 2 a Point prevalence of antibiotic use. b Period prevalence of antibiotic use. c Period prevalence of antibiotic use—last period before death. d Antibiotic use per infectious or feverish episode

decision, were associated with fewer antibiotic treatments in two articles [39, 41]. Other factors were only examined in one study.

Eating dependency, drinking insufficiently and being dehydrated, both before a LRI and at the time of the treatment decision, and swallowing difficulty decreased the likelihood of antibiotic treatment in the US and the Netherlands [41, 44]. Patients who had been diagnosed with pneumonia previously [41], and were more ADL (activities of daily living)-dependent [39], were also less likely to receive antibiotics. A high body temperature in the US and the Netherlands [44], and unstable vital signs in the US were positively related to antibiotic treatment for pneumonia [37].

Some articles showed contrasting results. Illness severity at the time of the treatment decision and 2 weeks before

the treatment decision related to withholding antibiotics in the Netherlands [41], but in the US, indicators of more severe acute illness were associated with more antibiotic prescriptions [39], or no association was found [44]. In addition, aspiration was associated with withholding antibiotics in the Netherlands [41], but in contrast, patients with suspected aspiration were more frequently treated with antibiotics in the US [37].

3.2.2 Persons Involved in Decision Making

Articles that reported factors associated with persons involved in decision making assessed attitudes of patients, families, and physicians in hypothetical scenarios, or in real-life situations using qualitative designs (Table 2 and

Table 1 Patient's health status factors associated with antibiotic use

Patient's health status factors									
Antibiotics	Factor ^a	Country	Setting	Limited to advanced dementia	Hypothetical ^b	Before death ^c	MMAT score	Usefulness	Study and year
	Pneumonia and symptoms								
AB ↑	Unstable vital signs	US	1675 bed LTCF	+	-	-	50%	useful	Chen et al., 2006
AB ↑	High temperature	US and NL	NHs	-	-	-	50%	useful	Szafara et al., 2012
AB ↑	Suspected aspiration	US	1675 bed LTCF	+	-	-	50%	useful	Chen et al., 2006
AB ↑	NO aspiration	NL	NHs	-	-	-	75%	useful	van der Steen et al., 2002
AB ↑	Illness severity US	US	NHs	-	-	-	100%	useful	Mehr et al., 2003
AB ↑(US) AB ↓(NL)	Illness severity at time of the treatment decision and 2 weeks before the treatment decision	US and NL NL	NHs NHs	- -	- -	- -	50% 75%	useful useful	Mehr et al., 2003 van der Steen et al., 2002
AB =	LRI severity in severe dementia	US and NL	NHs	-	-	-	50%	useful	Szafara et al., 2012
	Prognosis								
AB ↑	Approaching death (closer to death, determined in retrospect)	US	NHs	+	-	+	50%	useful	D'Agata and Mitchell, 2008
AB ↓	Poor prognosis (physician estimate at diagnosis) or ADEPT score	NL European countries and Israel	NHs NHs	- +	- -	- -	25% 75%	useful useful	van der Steen et al., 2009a [45] Onder et al., 2013
	Health status/condition								
AB ↓	ADL dependency	US and NL	NHs	-	-	-	100%	useful	Mehr et al., 2003
AB ↓	Previous pneumonia	NL	NHs	-	-	-	75%	useful	van der Steen et al., 2002
AB =	General health condition: increased urine of fecal incontinence, increased mobility dependence, increased illness severity, increased discomfort	NL	NHs	-	-	-	75%	useful	van der Steen et al., 2002
AB =	Vaccination for influenza in prior winter	NL	NHs	-	-	-	75%	useful	van der Steen et al., 2002
	Dietary intake								
AB ↓	Swallowing difficulty	US and NL	NHs	-	-	-	50%	useful	Szafara et al., 2012
AB ↓	Eating dependence - pre-LRI and at the time of the treatment decision	US and NL NL	NHs NHs	- -	- -	- -	50% 75%	useful useful	Szafara et al., 2012 van der Steen et al., 2002
AB ↓	Dehydration	NL	NHs	-	-	-	75%	useful	van der Steen et al., 2002
AB ↓	Insufficient drinking	NL	NHs	-	-	-	75%	useful	van der Steen et al., 2002
	Dementia status								
AB ↓	Increased level of severity of the dementia	US	NH, transitional care unit, assisted living unit	-	-	+	75%	useful	Gjerdingen et al., 1999
AB ↓	More severe dementia	US US and NL US and NL NL	Chronic care facilities NHs NHs NHs	- - - -	- - - -	- - - -	75% 100% 50% 75%	useful useful useful useful	Evers et al., 2002 Mehr et al., 2003 Szafara et al., 2012 van der Steen et al., 2002
AB =	Psychogeriatric disease: Alzheimer dementia, mixed dementia	NL	NHs	-	-	-	75%	useful	van der Steen et al., 2002

Highlighted rows factors reported in two or more articles

^a A definition or explanation of the factors is included in the electronic supplementary material

^b Hypothetical: factor from a study using a hypothetical scenario

^c Before death: factor from a study examining antibiotic use in the period before death

AB ↑ positive association with antibiotic treatment, AB ↓ negative association with antibiotic treatment, AB = no association with antibiotic treatment, ADEPT the Advanced Dementia Prognostic Tool, ADL activities of daily living, LRI lower respiratory infection, LTCF long-term care facility, MMAT Mixed Methods Appraisal Tool, NH nursing home, NL The Netherlands, US United States of America

ESM, online resource C, table 3). Four studies, conducted in the US and Australia, found that 47 % (71/152) [46], and 73 % (159/218; 38/52) [47, 48] of subjects deciding for themselves were willing to accept antibiotics in general, or specifically for the treatment of pneumonia. Agreeing to antibiotics depended on the severity of the dementia with percentages ranging from 74 % (62/84) choosing antibiotic treatment in the case of early Alzheimer's disease (AD) to only 25 % (21/84) in the case of severe or late AD in a US study [49].

Three articles assessed attitudes of family members of patients with dementia using a hypothetical scenario, and reported that a majority (range 60–90 %) preferred antibiotic treatment. The highest percentage was found in a US study reporting that 90 % (45/50) of spouses would choose antibiotics for their relative with dementia in case of a life-threatening infection [50]. In the case of critical illness (not further specified), 78 % (40/51) of Chinese family caregivers would agree with antibiotic treatment for their relative with dementia [51]. In a similar scenario, 60 % (30/50) of relatives would agree to oral antibiotics in the UK [52].

Other studies explored attitudes of families and physicians using qualitative designs. A US focus group study pointed out that family members encountered difficulties viewing pneumonia as part of a 'natural death' for someone with dementia, and easily agreed to aggressive treatment including intravenous antibiotics. In fact, antibiotics were viewed as a comfort measure, rather than as a technological way of prolonging life [53]. Furthermore, a US survey study found that while spouses were reasonably comfortable to forgo life-sustaining treatments such as CPR and feeding tubes, of all treatments spouses were the most comfortable with the decision to agree to antibiotics and the least comfortable with the decision to forego antibiotics [50].

A qualitative interview study that focused on the role of the physician found that physicians in the Netherlands have more patient contact and therefore know the patients and their relatives better than US physicians, and patient contact helped to start a timely discussion about treatment options for life-threatening infections. Ongoing care discussions before a 'crisis situation' occurs were thought to increase the odds of not choosing an aggressive treatment option [54]. Further, physicians preferred not to treat pneumonia when they considered treatment futile [45], and curative treatment was sometimes forgone with an explicit intention to hasten death [55].

3.2.3 Healthcare Context

The articles that described factors regarding the healthcare context indicated that patients living alone [46], and at

home, were more likely to receive antibiotics than nursing-home residents or hospital inpatients (Table 3) [19]. In Dutch nursing homes, the percentage of patients who received antibiotics for pneumonia increased with the number of psycho-geriatric beds in the facility [41]. The total number of beds or the number of beds for somatic patients was unrelated to antibiotic use for patients with dementia. Furthermore, antibiotic prescriptions were not related to the religious affiliation of the facility, urbanization level, the level of policy making or the availability of a protocol or policy on treatment or non-treatment [41]. Patients living in the Netherlands were less likely to receive antibiotic treatment than patients residing in the US [20]. Furthermore, patients who had a 'do not hospitalize' (DNH) order [37], or an advance directive [41, 56], were less likely to receive antibiotics.

Recommendations of a palliative care team aimed at improving comfort in a hospital did not affect antibiotic use in a US study [26]. In a recent Finnish article, an expert team comprising an infectious disease consultant and a geriatrician visited LTCFs and succeeded in reducing inappropriate use of antibiotics as UTI prophylaxis [23]. The factor time showed no association with antibiotic treatment, as observational studies in the US and the Netherlands found no change in antibiotic prescriptions over time in three and two death cohorts, respectively, between 1985 and 2007 [33, 40].

4 Discussion

To our best knowledge, this is the first review that systematically assesses the prevalence of antibiotic use among patients with dementia, and factors associated with antibiotic prescriptions in this population. Antibiotic use is often substantial (median 48 % within a median period of 14–30 days), but highly variable as the period prevalence ranged from 4.4 to 88 %. However, in attitudinal studies, many patients, families, and physicians prefer to forgo treatment. We found that more severe dementia and a poor prognosis were consistently associated with using less antibiotics in various countries. Associations with aspiration, illness severity, and a number of healthcare contextual factors differed by country.

4.1 Strengths and Limitations

We systematically identified, reviewed, and evaluated the literature concerning antibiotic use in patients with dementia. We considered the quality of the data in two ways, including only studies that met both general methodological criteria and usefulness criteria. The latter were developed because the first were rather unspecific and most

studies were not primarily aimed at examining the prevalence of antibiotic use and factors associated with it, but provided data that could be useful to some extent to address the research question of this review. Studies that were somewhat useful were only included when they met the minimum criteria for acceptable methodological quality.

Some limitations should be acknowledged. First, detailed information about the diagnosis of infections and the specific reason to prescribe antibiotics was mostly lacking. Second, we included studies when more than 50 % of subjects had dementia and some populations (4 of the 37 articles had less than 100 % dementia) were therefore not homogeneous. Third, because investigating associations with antibiotic use was often not the primary goal of the studies, only a few factors were examined in multiple articles, leaving little opportunity to compare between countries and settings. Fourth, we are aware of the fact that the findings of studies conducted in the Netherlands in nursing-home settings contributed substantially to the factors we identified as associated with antibiotic use. This indicates the importance of studying the factors associated with antibiotic treatment in countries other than the Netherlands. Last, articles that reported on attitudes of family and patients regarding antibiotics were among the oldest articles included, and often applied a hypothetical scenario or a qualitative approach using focus groups. This leaves room for discussion about what would be chosen in actual practice, and how valuable these results are to represent attitudes towards withholding treatment with antibiotics today. Over the last decades, attitudes regarding providing antibiotics for comfort may have changed and the involvement of patients themselves and family may have gained importance.

4.2 Variability in Antibiotic Use

The prevalence of antibiotic use varied widely between studies. Although the designs of the prevalence studies varied, antibiotic prescription patterns in practice probably also varied widely. Part of this variability is likely caused by little evidence being available on effects to guide practice. Furthermore, the decision about antibiotics may depend on country, setting, and on whether the patient is perceived as approaching the end of life. For example, we found that antibiotics were frequently prescribed in the last 30 days of life in Italy, but, in contrast, the point prevalence of antibiotic use in an earlier period was surprisingly low [19, 34].

4.3 Country and Setting

Studies comparing different countries after pooling individual patient data examined the situation in the US and in

the Netherlands. The few studies in other countries did not compare directly with other countries. Antibiotic use in general nursing-home populations varies between European countries; the mean point prevalence of antibiotic use ranged from 1.1 % in Latvia to 15.9 % in Finland [57]. Although this report lacks data about the prevalence in patients with dementia specifically, antibiotic use may be as variable, or perhaps even more variable in these patients.

US nursing-home residents, compared with Dutch residents, were more likely to receive antibiotics for pneumonia. Comparing both countries, the same factor operated in different directions: severity of the infection was associated with fewer antibiotics in the Netherlands, but increased antibiotic use in the US. Differences in training of physicians and differences in the organization of care may explain this. Dutch elderly care physicians follow a 3-year vocational training in elderly care medicine that includes training in advance care planning and decision making in end-of-life care [54, 58]. Further, elderly care physicians in the Netherlands are employed by the nursing home which is their principal site of practice. They therefore meet with their patients regularly, while, in many other countries and settings, care in the nursing home is provided by the general practitioner [58, 59]. Fewer physician contacts potentially result in less certainty about treatment decisions and family preferences, even after adjustment for country [60]. Physicians' experiences with treatment of patients with dementia, and with a focus on palliative care and withholding treatments, may also play a role.

Patients treated at home were more likely to receive antibiotics for an infection compared with patients in a hospital or nursing-home setting [19, 56]. It was suggested that the use of antibiotics at home may be higher due to urinary catheters, which were five times more common in patients living at home [19]. Furthermore, patients eligible for home care may have specific indications that relate to antibiotic use, such as infections or pressure sores. In many countries, hospitalization of patients with dementia and pneumonia is common and typically involves intravenous antibiotic treatment [61–63]. Treatments such as parenteral antibiotics—which may be the only treatment option for patients with intake problems—may not be available in a home-care or nursing-home setting, depending on the country, which implies that a decision for antibiotics sometimes parallels a decision to hospitalize.

Although few studies assessed cross-national variation in attitudes towards antibiotic treatment for patients with dementia, these attitudes and decision making probably differ. This is supported by variability in treatment decisions between physicians in different countries using hypothetical scenarios regarding chronically ill older patients. For example, 897 physicians from seven countries selected a treatment option from supportive care only to

Table 2 Person-related factors and associations with antibiotic use

Study	Antibiotics	Factor	Country	Setting	Limited to advanced dementia	Hypothetical ^a	Before death ^b	MMAT score (%)	Usefulness
Patient attitudes									
Mezey et al. [50]	AB ↑	Comfort of spouses with decision to forgo antibiotic was 40 % and lowest of all treatment decisions	US	Aging and dementia research center	-	+	-	50	Somewhat useful
Forbes et al. [23]	AB ↑	Antibiotics are viewed as a comfort measure, not as a technologic means of prolonging life for someone with severe dementia	US	NHs	-	-	-	75	Useful
Forbes et al. [53]	AB ↑	Many family members do not view pneumonia as part of a "natural death" for someone with dementia and agreed to hospitalization or to use of aggressive treatment in the nursing home, such as the use of IV antibiotics	US	NHs	-	-	-	75	Useful
Physician attitudes									
Helton et al. [54]	AB ↓	Value of QoL in decision making	US and NL	NHs	-	-	-	50	Useful
Helton et al. [54]	AB ↓	Knowing nursing home patients (physician)	US and NL	NHs	-	-	-	50	Useful
Helton et al. [54]	AB ↓	Discussing treatment options with family in a timely manner	US and NL	NHs	-	-	-	50	Useful
Helton et al. [54]	AB ↓	Responsibility for treatment decision making, NL vs US physicians	US and NL	NHs	-	-	-	50	Useful
van der Steen et al. [45]	AB ↓	Futility of treatment: physicians prefer not to treat when to do so seems futile	NL	NHs	-	-	-	25	Useful
van der Steen et al. [55]	AB ↓	Intention of hastening death	NL	NHs	-	-	-	25	Useful
Patient demographics									
Chen et al. [37]	AB ↑	Primary language not English	US	LTCF	+	-	-	50	Useful
Szafara et al. [44]	AB ↑	Gender (men)	US and NL	NHs	-	-	-	50	Useful
van der Steen et al. [20]	AB ↑	US residents vs NL residents	US and NL	NHs	-	-	-	100	Useful
van der Steen et al. [41]	AB =	Sex	NL	NHs	-	-	-	75	Useful
Physician demographics									
van der Steen et al. [45]	AB =	Physicians' experience, age, gender or training status	NL	NHs	-	-	-	25	Useful

There are no highlighted rows because there were no factors reported in two or more articles

^a Hypothetical: factor from a study using a hypothetical scenario

^b Before death: factor from a study examining antibiotic use in the period before death

AB ↑ positive association with antibiotic treatment, AB ↓ negative association with antibiotic treatment, AB = no association with antibiotic treatment, LTCF long-term care facility, MMAT Mixed Methods Appraisal Tool, NH nursing home, NL The Netherlands, QoL quality of life, US United States of America

Table 3 Healthcare contextual factors and associations with antibiotic use

References	Antibiotics	Factor	Country	Setting	Limited to advanced dementia	Hypothetical ^a	Before death ^b	MMAT score (%)	Usefulness
Advance directives									
Chen et al. [37]	AB ↓	A do not hospitalize (DNH) order	US	1,675-bed LTCF	+	–	–	50	Useful
van der Steen et al. [41]	AB ↓	Advance care planning	NL	NHs	–	–	–	50	Useful
Specifications of facilities									
Lo et al. [46]	AB ↑	Living alone	US	General internal medicine group practice	–	+	–	100	Somewhat useful
van der Steen et al. [41]	AB ↑	Number of psychiatric beds in the facility	NL	NHs	–	–	–	75	Useful
Toscani et al. [19]	AB ↑	Home care vs nursing homes or hospital	Italy	NHs and home care services	+	–	–	75	Useful
van der Steen et al. [41]	AB ↓	Treatment in the summer	NL	NHs	–	–	–	75	Useful
van der Steen et al. [41]	AB =	Nursing home situated in one of the three biggest NL cities	NL	NHs	–	–	–	75	Useful
van der Steen et al. [41]	AB =	Total number of beds or number of beds for somatic patients	NL	NHs	–	–	–	75	Useful
van der Steen et al. [41]	AB =	Religious affiliation of facility	NL	NHs	–	–	–	75	Useful
van der Steen et al. [41]	AB =	Level of policy making (availability of mission statement, quality policy, quality manual, and quality report on 4–point scale)	NL	NHs	–	–	–	75	Useful
van der Steen et al. [41]	AB =	Protocol or policy on (non) treatment available	NL	NHs	–	–	–	75	Useful
Interventions and guidelines									
Rummukainen et al. [23]	AB ↓	Intervention to reduce inappropriate use of antimicrobials in LTCFs using a team of experts visiting LTCFs	Finland	NHs and dementia units	–	–	–	75	Useful
Ahronheim et al. [26]	AB =	Recommendations by a palliative care team with the goal of enhancing patient comfort	US	Teaching hospital	–	–	–	50	Less useful
Other									
Evers et al. [33]	AB =	Time—three death cohorts (1985–1990; 1991–1995; 1996–2000)	US	Chronic care facilities	–	–	+	75	Useful
van der Steen et al. [40]	AB =	Time—two time cohorts (1996–1998; 2006–2007)	NL	NHs	–	–	–	50	Useful

There are no highlighted rows because there were no factors reported in two or more articles

^a Hypothetical: factor from a study using a hypothetical scenario

^b Before death: factor from a study examining antibiotic use in the period before death

AB ↑ positive association with antibiotic treatment, AB ↓ negative association with antibiotic treatment, AB = no association with antibiotic treatment, LTCF long-term care facility, MMAT Mixed Methods Appraisal Tool, NH nursing home, NL The Netherlands, US United States of America

maximum care including admission to the intensive care unit for an 82-year-old man with a gastrointestinal bleeding, and US physicians were among the most aggressive while Australian colleagues were the most conservative [64, 65].

4.4 Decision Making About Antibiotic Treatment

Most family members of patients with dementia would agree to antibiotic treatment for an infection. Many experience emotional difficulties including guilt when deciding to refrain from life-sustaining treatments [17], but being involved in decision making is not always regarded as a burden [66]. To avoid routinely prescribing antibiotics, one of the parties involved should initiate the discussion of withholding curative treatment [67]. Not only whether treatment options are being discussed, but also how they are addressed may make a difference. For example, in a US survey study, a detailed written explanation about pneumonia to inform community-dwelling older people about treatment options surprisingly led to more of the subjects choosing antibiotics in the case of severe dementia and pneumonia [68]. In practice, the physician's attitude may be important. That is, an attitude which is more passive and deferential to family preferences may result in more aggressive treatment (antibiotics and hospitalization), in contrast to an attitude to treat based on what is perceived by the physician to be in the best interest of the patient. This was observed in a study in which physicians in both the US and the Netherlands indicated that timely discussion of treatment options may decrease the risk of starting inappropriate treatment of pneumonia [54], emphasizing the importance of timely and effective communication between all parties involved in decision making.

4.5 Effects of Antibiotic Treatment: Ethical Considerations

The rationales behind withholding antibiotic treatment for terminally ill patients with dementia or incompetent patients and palliative use of antibiotics are the subject of an ethical debate in the literature [15, 69–74]. As the dementia progresses, the general treatment goal may shift from life prolongation to maintenance of function, and eventually to maximization of comfort [75]. However, the evidence base to guide treatment decisions about use of antibiotics consistent with these goals is small. In advanced dementia, antibiotics may prolong life in only a small minority of patients [76], but hydration status affected survival even more profoundly than antibiotic treatment in nursing-home residents, many of whom had dementia [44]. Antibiotics might also relieve the symptoms of pneumonia in the absence of other proper treatment to relieve

symptoms [77], and may be prescribed to provide comfort [41]. However, it remains unclear whether antibiotics actually enhance comfort, and if they do, whether such benefit outweighs the potential burden of antibiotic treatment in severely ill patients with dementia. Furthermore, one may consider that the patient, when cured of the infection, is still exposed to the deterioration of the dementia [78, 79]. When the goal of antibiotic treatment is not to provide comfort, and treatment is not expected to decrease mortality risk [42, 76], some question its usefulness. Others claim that, regardless of the underlying illness and potentially negative consequences, withholding a drug that is effective in a disease treatment is always inappropriate [80].

In decision making about providing antibiotics, prescribers may also consider their decision from a public health point of view and include the emergence of antibiotic resistance into their considerations to start or withhold treatment [69]. However, antibiotic resistance and inappropriate antibiotic use did not emerge as a factor from the studies we included in this review. This is not surprising, considering the novelty of the topic of antibiotic resistance, the limited awareness about it in, for example, the nursing home setting, and difficulty applying general knowledge about resistance in the community in individual cases in clinical practice [11, 69].

4.6 Implications

This review identifies several gaps in knowledge about the prevalence of antibiotic use in patients with dementia, as well as about factors associated with use of antibiotics in this population. The majority of articles focused on overall antibiotic use, or antibiotic use for RTIs, mostly in institutionalized patients (long-term care; hospital). Information about other common infections such as UTIs and skin infections, and about community-dwelling patients, is virtually lacking. Furthermore, few studies focused specifically on patients with advanced or end-stage dementia, and the factors investigated in these studies were not always the same as those assessed in studies that included all stages of dementia. Moreover, we found no studies that examined if factors associated with antibiotic use differed by dementia stage. Future studies should address these gaps, and distinguish types of infections and stages of dementia. We suggest a cross-national study in which a standardized set of factors as identified from our review is examined simultaneously and systematically, to further investigate antibiotic prescription patterns and how these may vary between countries and settings.

Little is known about attitudes and decision making in real practice situations. Qualitative studies using individual interviews or ethnographic designs may assess attitudes

among patients, family, healthcare workers, and physicians, and other factors that are important in decision making around antibiotics in practice. Observational studies about antibiotic use in patients with dementia should include the goal of antibiotic treatment, and investigate associations with function, survival, comfort, and quality of life in different settings to contribute to a more evidence-based approach in antibiotic use.

4.7 Conclusion

This review suggests that decision making about starting or withholding antibiotic treatment remains a challenge, involves ethical considerations, and is strongly influenced by the particular healthcare context. Treatment with antibiotics is sometimes withheld, but considerations about this, and perhaps whether use or non-use is considered at all, depend on country, setting, and family and physician preferences. This review provides a basis for further research and an international discussion among stakeholders about the ethical and practical considerations of withholding antibiotic treatment in patients with dementia.

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Conflict of interest We declare that there are no conflicts of interest.

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