



**QUEEN'S
UNIVERSITY
BELFAST**

Antimicrobial Use in Patients with Dementia: Current Concerns and Future Recommendations

Parsons, C., & van der Steen, J. T. (2017). Antimicrobial Use in Patients with Dementia: Current Concerns and Future Recommendations. DOI: 10.1007/s40263-017-0427-y

Published in:
CNS Drugs

Document Version:
Peer reviewed version

Queen's University Belfast - Research Portal:
[Link to publication record in Queen's University Belfast Research Portal](#)

Publisher rights

Copyright 2017 Springer International Publishing Switzerland.

This work is made available online in accordance with the publisher's policies. Please refer to any applicable terms of use of the publisher.

General rights

Copyright for the publications made accessible via the Queen's University Belfast Research Portal is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy

The Research Portal is Queen's institutional repository that provides access to Queen's research output. Every effort has been made to ensure that content in the Research Portal does not infringe any person's rights, or applicable UK laws. If you discover content in the Research Portal that you believe breaches copyright or violates any law, please contact openaccess@qub.ac.uk.

Antimicrobial Use in Patients with Dementia: Current Concerns and Future Recommendations

Carole Parsons PhD, and Jenny T. van der Steen, PhD

Carole Parsons PhD, School of Pharmacy, 97 Lisburn Road, Belfast, Queen's University Belfast, BT9 7BL, United Kingdom. Email: c.parsons@qub.ac.uk; Telephone: +44 (0) 28 9097 2304; Fax: +44 (0) 28 9024 7794

Jenny T. van der Steen, PhD, (1) Leiden University Medical Center, Department of Public Health and Primary Care, Hippocratespad 21, Gebouw 3, P.O. Box 9600, 2300 RC Leiden, The Netherlands; Email jtvandersteen@lumc.nl; Telephone +31-71-5268456

(2) Radboud university medical center, Department of Primary and Community Care (117 ELG), Geert Grooteplein Noord 21, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands

Email during submission process (I kept the account of my former employer): j.vandersteen@vumc.nl

Word count manuscript: 2528

Word count abstract: 160 words

Funding/Support: JTvdS is supported by a career award from the Netherlands Organisation for Scientific Research (NWO; Innovational Research Incentives Scheme) Vidi grant number 91711339. No funding source is reported for Dr. Parsons

For correspondence:

Carole Parsons PhD, School of Pharmacy, 97 Lisburn Road, Belfast, Queen's University Belfast, BT9 7BL, United Kingdom. Email: c.parsons@qub.ac.uk; Telephone: +44 (0) 28 9097 2304; Fax: +44 (0) 28 9024 7794

Abstract

Infections are common in people with dementia, and antibiotic use is widespread although highly variable across healthcare settings and countries. The few studies conducted to date which consider the appropriateness of antibiotic prescribing specifically for people with dementia focus on people with advanced dementia and suggest that much of the prescribing of antibiotics for these patients may be potentially inappropriate. We suggest that clinicians must consider a number of factors to determine appropriateness of antimicrobial prescribing for people with dementia, including the risks and benefits of assessing and treating infections, the uncertainty regarding the effects of antibiotics on patient comfort, goals of care and treatment preferences, hydration status, dementia severity, and patient prognosis. Future research should examine antibiotic prescribing and its appropriateness across the spectrum of common infections, dementia severities, care settings and countries, and should consider how antibiotic therapy should be considered in discussions regarding treatment preferences, goals of care and/or advance care planning, between clinicians, patients and families.

Keypoints

- Antibiotic use in people in dementia is influenced by a wide variety of clinical and non-clinical factors such as burden of treatment, illness severity and family preferences;
- Antibiotic use may frequently be inappropriate, but in dementia, assessment of appropriateness is more difficult due to, for example, difficulties in diagnosis and communicating symptoms;
- Future research may develop consensus guidelines on appropriate prescribing of antibiotics that may be contextualised locally

1. Introduction

Dementia is an irreversible progressive neurodegenerative disorder in which widespread neuronal cell death results in decline across a range of cognitive domains including difficulties in memory, disturbances in language, psychosocial and psychiatric changes, loss of ability to recognise familiar people or common objects, and impairment in activities of daily living [1-3]. It has been renamed “major neurocognitive disorder” in the most recent edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [3] in an effort to reduce stigma associated with dementia, to bring diagnostic guidelines into line with current clinical practice, and in recognition of earlier stages of cognitive decline as mild neurocognitive disorder (NCD) [4].

There are many aetiological variants of dementia, distinguished by unique neuropathology and determined by the area or structure within the brain predominantly affected [5]. Alzheimer’s disease (AD) is the most common variant, followed by vascular dementia (VaD). There is considerable overlap between AD and VaD; the amyloid plaques and neurofibrillary tangles associated with AD often co-exist with the multiple infarctions present in VaD and where this occurs, patients are diagnosed with mixed dementia [6,7]. Though AD and VaD are the most common variants to co-exist in mixed dementia, the term may be used to refer to the presence of two or more of any of the aetiological variants of dementia. Dementia with Lewy Bodies (DLB) and Frontotemporal Dementia (FTD) are less common variants which account for much smaller percentages of diagnosed cases.

The World Alzheimer Report published in 2015 estimated that 46.8 million people worldwide are living with dementia, and this number is expected to almost double every 20 years, reaching 74.7 million in 2030 and 131.5 million in 2050 [8]. Infections, including respiratory tract infections (RTIs), urinary tract infections (UTIs), and skin and soft tissue infections [9,10], are common in people with dementia. Treatment decisions for these vulnerable patients are often highly complex, particularly as dementia progresses and patients approach end of life [11], due to the inability of patients to communicate their symptoms as cognitive function declines, and because typical symptoms of infections are often absent [12,13]. Such decisions typically involve balancing potential benefits and burdens of treatment, patient and family preferences, the best interests of the patient and the risk of developing antibiotic resistant microbes [14-17]. A recent systematic review by van der Maaden and colleagues substantiated the view in the literature that decisions to start or withhold antibiotic treatment are challenging, identifying over 40 person- and context-related factors associated with antibiotic use in this population. The authors reported that these decisions are strongly influenced by country, healthcare context, and family and physician preferences [11].

The variability in antibiotic prescribing rates and practices across dementia severity, healthcare settings and countries may be due to the complexity of treatment decisions about antibiotics in dementia, in addition to limitations in certain care settings (such as the absence of diagnostic resources in long-term care environments) and a limited and somewhat contradictory evidence-base on the effects of antibiotic use [11,18,19]. The objectives of this narrative review are to consider the most common infections in people with dementia, and the treatment of such infections in this vulnerable patient group. We will also consider appropriate use (and misuse) of antimicrobials, and the variations in prescribing and care including at the end of life, with a particular focus on the long-term care setting to reflect the majority of the research literature in this area. Finally, we will make recommendations for practice and highlight research priorities for future studies in this area.

2. Infections in older people with dementia

Immune senescence (age-associated changes in innate and adaptive immunity), physiological changes such as decreased nutritional status, development of swallowing difficulties and reduced mucociliary clearance, and frailty (defined as a state of increased vulnerability to poor resolution of homeostasis after a stressor event [20]), predispose older people to infection [21-23]. Furthermore, the aging process can complicate the diagnosis and treatment of infectious disease; fever and increased white cell counts tend to be less pronounced, and this can result in infections remaining undiagnosed [24]. Age-related changes in pharmacokinetics of antibiotics can alter absorption, distribution and elimination of these drugs, rendering treatment less effective or increasing the risk of toxicity [25-27]. As a consequence, older people are not only at increased risk of developing infections including lower respiratory tract infections (LRTIs, pneumonia), urinary tract infections (UTIs), and skin and soft tissue infections, but are also more likely to experience misdiagnosis and mismanagement [23]. Diagnosis is further complicated by the difficulty in obtaining good quality uncontaminated clinical specimens from older people, particularly from those who are unable to comply with the directions for obtaining such a sample. Although the risk of developing pneumonia is not significantly higher for people with dementia than for cognitively intact frail older people [28-30], diagnosis is more difficult, particularly in the more advanced stages of dementia, and risks of misdiagnosis and mismanagement are further increased. These individuals are more likely to experience delay in recognition of changes in status which would prompt assessment for infection, and have increased risk of mortality, both in general [31,32] or due to an infection [33-36]. A systematic review and meta-analysis to determine whether people with dementia were more likely to die from pneumonia as the immediate or underlying cause reported that the odds of pneumonia-associated mortality were increased more than two-fold for people with dementia [33]. Dysphagia has been recognised as a risk factor for pneumonia in people with dementia [37], and pneumonia and intake problems are important risk factors for mortality across all stages of dementia [9,38]. Studies focusing on advanced dementia have reported an association between dysphagia and aspiration pneumonia [39], and have demonstrated that pneumonia is significantly associated with shortened survival of nursing home residents [34,40]. It has been suggested that increased mortality of pneumonia in advanced dementia is associated with aspiration and weight loss [41], and with artificial feeding via the enteral route [42].

Antibiotics are widely prescribed for older people with dementia; most studies of prevalence of antibiotic use conducted to date consider the long-term care setting, with a smaller number examining hospital or community-dwelling settings [11]. These studies assessed prevalence of antibiotic use in a variety of ways, including: point prevalence, period prevalence, antibiotic use in the last period before death, and antibiotic use during a specific infectious episode. Acknowledging the range of the methods used in the included studies, the authors reported that antibiotic use for people with dementia is often substantial but highly variable across healthcare contexts and countries. Point prevalence ranged from 3.3 to 16.6%, with period prevalence ranging from 4.4 to 88% overall, and from 23.5 to 94% in variable time frames before death. The median use was reported to be 52% for a median period of 14 days, and 48% for a median period of 22 days respectively. Antibiotics were prescribed for most patients with LRTIs or UTIs; between 77 and 91% of patients received treatment. The authors also found that more severe dementia was associated with lower rates of antibiotic use [11]. Poor prognosis was also associated with antibiotic use, and the direction of this association was dependent on the country of care.

Patients with a poor prognosis were more likely to receive antibiotics in studies conducted in the US [43,44] and across seven European countries and Israel [45]. Conversely people with a poor prognosis were more likely to not have antibiotics prescribed in the Netherlands [44].

3. Appropriateness of antibiotic use

In considering antimicrobial prescribing for people with dementia, it is important to not only examine the prevalence of such prescribing but also whether it is appropriate. Prescribing is considered to be appropriate when medicines have a clear evidence-based indication, are cost-effective and well-tolerated [46]. Terms such as “inappropriate medication use”, “inappropriate drug use (IDU)”, “inappropriate prescribing (IP)” and “potentially inappropriate prescribing (PIP)” are used throughout the literature to refer to suboptimal prescribing practices which include misprescribing, overprescribing or underprescribing of medications [47,48]. A significant body of research exists which examines the appropriateness of antimicrobial use in older people residing in long-term care settings; however, there has been limited work undertaken to date which examines the appropriateness of antibiotic prescribing specifically in people with dementia [49,50].

The few studies conducted to date which do consider appropriateness of antibiotic use in people with dementia focus on the advanced stages of disease; one study of US nursing home residents reported that 44% of suspected infectious episodes for which antimicrobials were prescribed met minimum clinical criteria [18], suggesting that much of the prescribing of antibiotics in advanced dementia may be unwarranted [50]. The authors concluded that antibiotics were most likely to be initiated in the absence of minimum treatment criteria for UTIs which rely on subjective signs and symptoms undetectable to the observer in the absence of patient self-report. They recognised that, while asymptomatic bacteriuria is the most common reason for potentially inappropriate antimicrobial prescribing in the nursing home setting, the interpretation of what is “symptomatic” in people in advanced dementia, and therefore the application of minimum criteria for treatment, are particularly challenging [50].

4. Recommendations for clinical practice

In clinical practice, a number of factors must be taken into account when considering the appropriateness of antimicrobial treatment for this vulnerable patient group. Consideration should not be limited to whether treatment should be initiated. Further aspects must be considered, such as whether a particular medication should be chosen based on the infection being treated, and the local patterns of antimicrobial susceptibility and resistance, in addition to whether treatment should be changed or continued based on clinical response or results of culture and diagnostic testing, Length of treatment, route of administration (oral versus intravenous), and the wishes and preferences of the patient and their family are also important considerations in determining appropriateness of antimicrobial prescribing.

Clinicians must take into account many factors when making decisions regarding antimicrobial prescribing for people with dementia. Firstly, antibiotic therapy in the terminal stages of dementia prolongs survival in very few patients; indeed it has been argued that it may simply prolong the dying process [51,52]. Secondly, there is uncertainty as to whether antibiotics play a significant role in the maintenance of comfort in people with dementia suffering from pneumonia; a study of 323 nursing home residents with advanced dementia in 22 US nursing homes considered symptoms before, during and after pneumonia and reported that treatment with

antimicrobial agents does not improve comfort (symptom burden) of residents with advanced dementia who have pneumonia. It is important to note that in this study, comfort was assessed on one occasion during a three-month period which included the episode of pneumonia. [53]. In contrast to the work by Volicer & Simard [51] and van der Steen *et al.* [52], Givens *et al.* [53] also reported prolonged survival among patients who received antibiotics compared to those for whom antibiotics were not prescribed. Others have argued that antibiotic treatment is associated with improved comfort [54], and more recent work suggests that antibiotics may not make a difference in comfort levels if effective symptom relief is provided [55]. Antibiotics may be prescribed because physicians and family members believe that antibiotics improve patient comfort [56,57]. Further, antibiotic use may be associated with significant adverse effects, such as gastrointestinal upset, allergic reactions, hyperkalaemia, and rarely, agranulocytosis; overuse may lead to *Clostridium difficile* infection and development of antimicrobial resistance to treatment [51].

A decision to treat a patient with signs and symptoms suggestive of infection may not necessarily require the prescribing of antibiotic therapy. Such a decision may be made in the context of consideration of goals of care, or may be based on a conservative therapeutic approach involving watchful waiting, and may therefore be revisited as a patient is offered symptomatic relief and supportive care including pain management, skin care, and hydration. The interplay of the factors outlined above complicates the clinical decision-making process regarding appropriateness of antimicrobial therapy for this patient group. Decisions to prescribe or withhold antibiotics in advanced stages should take into consideration the risks and benefits of assessing and treating infections, the uncertainty regarding any significant benefits of treatment for patient comfort, and should align such considerations with goals of care [50,51]. If a decision is reached to withhold antibiotics, suspected infections should not be worked up, and symptoms treated using palliative measures alone [50].

Furthermore, clinicians must also bear in mind the hydration status of the patient due to its impact on the effectiveness of antibiotic therapy. Similar mortality rates have been reported for nursing home residents who had sufficient water intake whether or not they were prescribed antibiotics [51,52,58]. Conversely, in a two-country study, antibiotics have been shown to be less effective for nursing home residents who had insufficient water intake, and mortality rates reported to be highest for residents who neither received antibiotics nor had sufficient water intake [58].

Optimising the management of infections in people with dementia is of critical importance, requiring collaboration between geriatrics and infectious disease specialists, and in the more advanced stages of dementia, palliative care experts [59]. It should include patient and family counselling, clinical training and the development and/or utilisation of clinical algorithms to evaluate appropriateness of antimicrobial prescribing which take into consideration dementia severity, patient prognosis, goals and burden of care and treatment preferences as appropriate [17,59-61].

5. Research priorities

To date, studies considering prevalence of antibiotic use in people with dementia have focused on people with advanced stages of the disease residing in long-term care or hospital settings, and have not considered common infections such as skin or soft tissue infections [11]. Further work examining antibiotic prescribing across the

spectrum of common infections (UTIs, LRTIs and skin and soft tissue infections), dementia severities, and care settings (long-term care, hospital and community-dwelling), is therefore a research priority.

Studies examining the appropriateness of antibiotic prescribing for older people in nursing homes have used a number of different algorithms to date [62]; it has been suggested that a universally applicable instrument to facilitate international comparison should be developed, which accounts for country-specific practice variations and into which existing guidelines and articles on appropriate prescribing of antibiotics [63-68] and patient preference and prognosis [62] could be incorporated. Whilst these guidelines are not specific to people with dementia, it has been argued that in developing such an instrument, applicability should be ensured across long-term care facilities and countries, and also in residents of such facilities with dementia [13]. Future research should therefore focus on the development of such an instrument, and should consider discussions between clinicians, patients and families regarding antibiotic treatment preferences, goals of care and/or advance care planning. There is also a need to define appropriate outcomes to be employed in randomised controlled trials of antimicrobials in people with dementia, particularly in relation to (dis)comfort measures.

6. Conclusion

Infections are common among people with dementia, and prescribing of antibiotics is prevalent, though highly variable across settings of care and across countries. The appropriateness of such prescribing has been neglected in the research literature to date. Further studies into prevalence and appropriateness of antibiotic prescribing across the spectrum of common infections, dementia severities, care settings and countries is a research priority.

Conflict of interest

Authors Parsons and van der Steen declare that they have no conflicts of interest.

References

1. Burns, A. and Iliffe, S. Dementia. *BMJ*. 2009;338:405-9.
2. National Institute for Health and Care Excellence. Dementia: supporting people with dementia and their carers in health and social care. NICE clinical guideline 42. [Online] London: NICE, 2016 Available at: <https://www.nice.org.uk/guidance/cg42?unlid=9429054072016126125418> [Accessed 2nd March 2017]
3. American Psychiatric Association Diagnostic and statistical manual of mental disorders. 5th Edition. Arlington, VA: American Psychiatric Publishing (2013)
4. Alzheimer's Australia. Diagnostic criteria for dementia. Available at: https://www.fightdementia.org.au/files/helpsheets/Helpsheet-DementiaQandA11-DiagnosticCriteriaForDementia_english.pdf [Accessed 13th March 2017]
5. World Health Organisation International statistical classification of diseases and related health problems: 10th Revision. [Online] Geneva: WHO, 2016. Available at: <http://apps.who.int/classifications/icd10/browse/2016/en#/F00-F09> [Accessed on 13th March 2017]
6. Massoud F, Devi G, Stern Y, Lawton A, Goldman JE, Liu Y, et al. A clinicopathological comparison of community-based and clinic-based cohorts of patients with dementia. *Arch Neurol*. 1999;56:1368-73.

7. Langa KM, Foster NL, Larson EB Mixed dementia: emerging concepts and therapeutic implication. *JAMA*. 2004;292:2901–8.
8. Prince M, Wimo A, Guerchet D, Ali G, Wu Y, Prina M. World Alzheimer Report; the global impact of dementia, an analysis of prevalence, incidence, costs and trends. Alzheimer’s Disease International (ADI), London, 2015.
9. Mitchell SL, Teno JM, Kiely DK, Shaffer ML, Jones RN, Prigerson HG, et al. The clinical course of advanced dementia. *N Engl J Med*. 2009;361(16):1529-38.
10. Vandervoort A, Van Den Block L, van der Steen JT, Volicer L, Vander Stichele R, Houttekier D, et al. Nursing home residents dying with dementia in Flanders, Belgium: a nationwide post-mortem study on clinical characteristics and quality of dying. *J Am Med Dir Assoc*. 2013;14 (7):485-92.
11. van der Maaden T, Hendriks SA, de Vet HCW, Zomerhuis MT, Smalbrugge M, Jansma EP, et al. Antibiotic use and associated factors in patients with dementia: a systematic review. *Drugs Aging*. 2015;32 (1):43-56.
12. Scherder E, Herr K, Pickering G. Pain in dementia. *Pain*. 2009;14(3):276-8.
13. D’Agata E, Loeb MB, Mitchell SL. Challenges in assessing nursing home residents with advanced dementia for suspected urinary tract infections. *J Am Geriatr Soc*. 2013;61(1):62-6.
14. van Buul LW, van der Steen JT, Veenhuizen RB, Achterberg WP, Schellevis FG, Essink RT, et al. Antibiotic use and resistance in long term care facilities. *J Am Med Dir Assoc*. 2015;13(6):568.e1-13.
15. Croft AC, D’Antoni AV, Terzulli SL. Update on the antibacterial resistance crisis. *Med Sci Monit*. 2007;13(6):RA103-18.
16. Hurley AC, Volicer L. Alzheimer Disease: “It’s okay, Mama, if you want to go, it’s okay”. *JAMA*. 2002;288(18):2324-31.
17. van der Steen JT, Ooms ME, Ribbe MW, van der Wal G. Decisions to treat or not to treat pneumonia in demented psychogeriatric nursing home residents: evaluation of a guideline. *Alzheimer Dis Assoc Disord*. 2001;15(3):119-28.
18. Loeb M, Simor AE, Landry L, Walter S, McArthur M, Duffy J, et al.. Antibiotic use in Ontario facilities that provide chronic care. *J Gen Intern Med*. 2001;16(6):376-83.
19. Zimmer JG, Bentley DW, Valenti WM, Watson NM. Systemic antibiotic use in nursing homes. A quality assessment. *J Am Geriatr Soc*. 1986;34(10):703-10.
20. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet*. 2013;381:752-62
21. Giefing-Kroll C, Berger P, Lepperdinger G, Grubeck-Loebenstien B. How sex and age affect immune responses, susceptibility to infections, and response to vaccination. *Aging Cell*. 2015;14:309-21.
22. Montgomery RR, Shaw AC. Paradoxical changes in innate immunity in aging: recent progress and new directions. *J Leukoc Biol*. 2015; 98(6):937-43.
23. Kline KA, Bowdish DME. Infection in an aging population. *Curr Opin Microbiol*. 2016;26:63-7.
24. Mouton SP, Bazaldua OV, Pierce B, Espino DV. Common infections in older adults. *Am Fam Physician*. 2001;63:256-68.
25. Bradley SF. Principles of antimicrobial therapy in older adults. *Clin Geriatr Med*. 2016;32:443-57.
26. Mangoni AA, Jackson SHD. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol*. 2004;57(1): 6-14.
27. Meyers BR, Wilkinson P. Clinical pharmacokinetics of antibacterial drugs in the elderly: implications for selection and dosage. *Clin Pharmacokinet*. 1989;17:385-95.

28. Eikelenboom-Boskamp A, Cox-Claessens HM, Boom-Poels PGM, Drabbe MIJ, Koopmans RTCM, Voss A. Three-year prevalence of healthcare-associated infections in Dutch nursing homes. *J Hosp Infect.* 2011;78:59-62.
29. Magaziner J, Zimmerman S, Gruber-Baldini AL, van Doorn C, Hebel JR, German P, et al. Mortality and adverse health events in newly admitted nursing home residents with and without dementia. *J Am Geriatr Soc.* 2005;53(11):1858-66.
30. Eriksen HM, Iversen BG, Aavitsland P. Prevalence of nosocomial infections and use of antibiotics in long-term care facilities in Norway. 2002 and 2003. *J Hosp Infect.* 2004;57:316-20.
31. Thomas JM, Cooney LM, Fried T. Systematic review: Health-related characteristics of elderly hospitalized adults and nursing home residents associated with short-term mortality. *J Am Geriatr Soc.* 2013;61(6):902-11.
32. Sachs GA, Carter R, Holtz LR, Smith F, Stump TE, Tu W, et al. Cognitive impairment: an independent predictor of excess mortality. *Ann Intern Med.* 2011; 15:300-8.
33. Foley NC, Affoo RH, Martin RE. A systematic review and meta-analysis examining pneumonia-associated mortality in dementia. *Dement Geriatr Cogn Disord.* 2015;39:52-67.
34. Naughton BJ, Mylotte JM, Tayara A. Outcome of nursing home-acquired pneumonia: derivation and application of a practical model to predict 30 day mortality. *J Am Geriatr Soc.* 2000;48(10):1292-1299
35. Volicer BJ, Hulrey A, Fabiszewski KJ, Montgomery P, Volicer L. Predicting short-term survival for patients with advanced Alzheimer's disease. *J Am Geriatr Soc.* 1993;41:535-40.
36. Fabiszewski KJ, Volicer B, Volicer L. Effect of antibiotic treatment on outcome of fevers in institutionalized Alzheimer patients. *JAMA.* 1990;263:3168-72.
37. Cabré M, Serra-Prat M, Force L, Almirall J, Palomera E, Clavé P. Oropharyngeal dysphagia is a risk factor for readmission for pneumonia in the very elderly persons: observational prospective study. *J Gerontol A Biol Sci Med Sci.* 2014;69(3):330-7.
38. Hendricks SA, Smalbrugge M, van Gageldonk-Lafeber AB, Galindo-Garre F, Schipper M, Hertogh CPM, et al. Pneumonia, intake problems, and survival among nursing home residents with variable stages of dementia in the Netherlands. *Alzheimer Dis Assoc Disorder.* 2016; Epub ahead of print 15th November 2016; doi: 10.1097/WAD.0000000000000171
39. 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 Directors Assoc.* 2011;12:344-54.
40. Hicks KL, Rabins PV, Black BS. Predictors of mortality in nursing home residents with advanced dementia. *Am J Alzheimers Dis Other Demen.* 2010;25(5):439-45.
41. van der Steen JT, Ooms ME, Mehr DR, van der Wal G, Ribbe MW. Severe dementia and adverse outcomes of nursing home-acquired pneumonia: evidence for mediation by functional and pathophysiological decline. *J Am Geriatr Soc.* 2002;50:439-48.
42. Cintra MTG, De Rezende NA, De Moraes EN, Cunha LCM, Da Gama Torres HP. A comparison of survival, pneumonia, and hospitalization in patients with advanced dementia and dysphagia receiving either oral or enteral nutrition. *J Nutr Health Aging.* 2014;18(10):894-9.
43. D'Agata E, Mitchell SL. Patterns of antimicrobial use among nursing home residents with advanced dementia. *Arch Intern Med.* 2008;168(4):357-62.
44. van der Steen JT, Kruse RL, Ooms ME, Ribbe MW, van der Wal G, Heintz LL, et al. Treatment of nursing home residents with dementia and lower respiratory tract infection in the United States and the Netherlands: an ocean apart. *J Am Geriatr Soc.* 2004;52:691-99.

45. Onder G, Liperoti R, Foebel A, Fialova D, Topinkova E, van der Roest HG, et al. Polypharmacy and mortality among nursing home residents with advanced cognitive impairment: results from the SHELTER Study. *J Am Med Dir Assoc.* 2013; 14 (6):450.e7-12.
46. O'Mahony D, Gallagher PF. Inappropriate prescribing in the older population: need for new criteria. *Age Ageing.* 2008; 37(2):138-41.
47. Kaufmann CP, Tremp R, Hersberger KE, Lampert ML. Inappropriate prescribing: a systematic review of published assessment tools. *Eur J Clin Pharmacol.* 2014;70(1):1-11.
48. Spinewine A, Schmader KE, Barber N, Hughes C, Lapane KL, Swine C et al. Appropriate prescribing in elderly people: how well can it be measured and optimised? *Lancet.* 2007;370(9582): 173-84.
49. Parsons C. Polypharmacy and inappropriate medication use in patients with dementia: an under-researched problem. *Ther Adv Drug Saf.* 2016; doi:10.1177/2042098616670798
50. Mitchell SL, Shaffer ML, Loeb MB, Givens JL, Habtemariam D, Kiely DK et al. Infection management and multi-drug resistant organisms in nursing home residents with advanced dementia. *JAMA Intern Med.* 2014;174(10):1660-67.
51. Volicer L, Simard J. Palliative care and quality of life for people with dementia: medical and psychosocial interventions. *Int Psychogeriatr.* 2015;27(10):1623-34.
52. van der Steen JT, Lane P, Kowall NW, Knol DL, Volicer L. Antibiotics and mortality in patients with lower respiratory infection and advanced dementia. *J Am Med Dir Assoc.* 2012;13:156-61.
53. Givens JL, Jones RN, Shaffer ML, Kiely DK, Mitchell SL. Survival and comfort after treatment of pneumonia in advanced dementia. *Arch Intern Med.* 2010;170(13):1102-7.
54. van der Steen JT, Pasman HRW, Ribbe MW, van de Wal G, Onwuteaka-Philipsen BD. Discomfort in dementia patients dying from pneumonia and its relief by antibiotics. *Scand J Infect Dis.* 2009;41(2):143-51.38.
55. van der Maaden T, van der Steen JT, de Vet HCW, Hertogh CPM, Koopmans RTCM. Prospective observations of discomfort, pain, and dyspnea in nursing home residents with dementia and pneumonia. *J Am Med Dir Assoc.* 2016;17:128-35.
56. van der Steen JT, Ooms ME, Adèr H, Ribbe MW, van der Wal G. Withholding antibiotic treatment in pneumonia patients with dementia; a quantitative observational study. *Arch Intern Med.* 2002;162(26):1753-60.
57. Forbes S, Bern-Klug M, Gessert C. End-of-life decision making for nursing home residents with dementia. *J Nurs Scholarship.* 2000;32(3):251-8.
58. Sfazara KL, Kruse RL, Mehr DR, Ribbe MW, van der Steen JT. Mortality following nursing home-acquired lower respiratory tract infection: LRI severity, antibiotic treatment, and water intake. *J Am Med Dir Assoc.* 2012;13:376-83.
59. Juthani-Mehta M, Malani PN, Mitchell SL. Antimicrobials at the end of life: an opportunity to improve palliative care and infection management. *JAMA.* 2015;314(19):2017-8.
60. van der Steen JT, Radbruch L, Hertogh CPM, de Boer ME, Hughes JC, Larkin P, et al. White paper defining optimal palliative care in older people with dementia: a Delphi study and recommendations from the European Association for Palliative Care. *Palliat Med.* 2014;28(3):197-209.
61. van der Steen JT, Muller MT, Ooms ME, van der Wal G, Ribbe MW. Decisions to treat or not to treat pneumonia in demented psychogeriatric nursing home patients: development of a guideline. *J Med Ethics.* 2000; 26 (2): 114-20.
62. van Buul LW, Veenhuizen RB, Achterberg WP, Schellevis FG, Essink RT, de Greeff SC, et al. Antibiotic prescribing in Dutch nursing homes: how appropriate is it? *J Am Med Dir Assoc.* 2015;16(3):229-37.
63. Lim CJ, King DCM, Stuart RL. Reducing inappropriate antibiotic prescribing in the residential care setting: current perspectives. *Clin Interv Aging.* 2014;9:165-77.

64. Zimmerman S, Sloane PD, Bertrand R, et al. Successfully reducing antibiotic prescribing in nursing homes. *J Am Geriatr Soc.* 2014; 62:907-12.
65. High KP, Bradley SF, Gravenstein S, Mehr DR, Quagliarello VJ, Richards C, et al. Clinical practice guideline for the evaluation of fever and infection in older adult residents of long-term care facilities: 2008 update by the Infectious Diseases Society of America. *J Am Geriatr Soc.* 2009;57:375-94.
66. Loeb M, Bentley DW, Bradley S, Crossley K, Garibaldi R, Gantz N, et al. Development of minimum criteria for the initiation of antibiotics in residents of long-term care facilities: results of a consensus conference. *Infect Control Hosp Epidemiol.* 2001;22:120-4.
67. Nicolle LE, Bentley DW, Garibaldi R, Neuhaus EG, Smith PW. Antimicrobial use in long-term care facilities. SHEA Long-Term-Care Committee. *Infect Control Hosp Epidemiol.* 2000;21:527-45.
68. Gyssens IC, van der Broek PJ, Kullberg BJ, Hekster Y, van der Meer JW. Optimizing antimicrobial therapy. A method for antimicrobial drug use evaluation. *J Antimicrob Chemother.* 1992;30:724-7.