National Clinical Guideline Centre

Pneumonia

Diagnosis and management of community- and hospital-acquired pneumonia in adults

Clinical guideline <…>

Appendix H

June 2014

Draft for consultation

Commissioned by the National Institute for Health and Care Excellence

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

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1. CAP

1.1 Diagnostic tests

No economic evidence was identified.

1.2 Severity assessment

No economic evidence was identified.

1.3 Microbiological tests

Table 1: FALGUERA2010

Falguera M, Ruiz-Gonzalez A, Schoenenberger JA, Touzon C, Gazquez I, Galindo C et al. Prospective, randomised study to compare empirical treatment versus targeted treatment on the basis of the urine antigen results in hospitalised patients with community-acquired pneumonia. Thorax. 2010; 65(2):101-106. (Guideline Ref ID FALGUERA2010)				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CCA (health outcomes = death, clinical relapse, admission to IYU, length of hospital stay, readmission, adverse events, length of antimicrobial treatment) **Study design:** Prospective, randomised, comparative trial. **Approach to analysis:** Within trial analysis **Perspective:** Spanish hospital **Follow up:** One month **Treatment effect duration:** NA	**Population:** Adults with high-severity CAP **Patient Characteristics:** Start age = 64.5 M =58.5 n = 157 **Treatment on admission:** Either: Option 1) IV beta-lactam (ceftriaxone, 2 g daily, or co-amoxiclav, 1 g t.i.d.) plus IV macrolide (azithromycin, 500 mg daily) Option 2) IV fluoroquinolone (levofloxacin, 750 mg daily) **Intervention 1:** Empirical treatment: If patients were treated with option 1 above they were switched to oral beta-lactam (co-amoxiclav, 875/125mg, t.i.d. or cefditoren, 400 mg	**Total costs (mean per patient):** Intvn 1: £1,359 Intvn 2: £1,327 Incremental (2-1):£33 (CI NR; p = 0.28) **Currency & cost year:** 2009 Euros (presented here as 2009 UK pounds‡) **Cost components incorporated:** Hospital stay Antimicrobials Diagnostic procedures	**Deaths (mean per patient):** Intvn 1: 0 Intvn 2: 0.0114 Incremental (2-1): 0.0114 (CI NR; p = 0.50) **Clinical relapses (mean per patient):** Intvn 1: 0.0225 Intvn 2: 0.0455 Incremental (2-1): 0.0230 (CI NR; p = 0.44) **Admission to ICU (mean per patient):** Intvn 1: 0.0112 Intvn 2: 0 Incremental (2-1): -0.0112 (CI NR; p = 1.00) **Length of stay, days (mean per patient):** Intvn 1: 7.1 ± 3.8 Intvn 2: 7.1 ± 4.0	**ICER (Intvn 2 vs Intvn 1):** NA CI: NA Probability Intvn 2 cost effective (£20K/30K threshold): NA **Analysis of uncertainty:** NA

Discounting: Costs = NA ; Outcomes = NA	b.d) to complete a 10-day course, plus oral macrolide (azithromycin, 500 mg daily) to complete 5 days of treatment If patients were treated with option 2 above they were switched to oral fluoroquinolone (levofloxacin, 750 mg daily) to complete a 10-day course **Intervention 2:** Targeted treatment If pneumococcal urine antigen positive: switched to oral amoxicillin, 1 g t.i.d, to complete a 10-day course If legionella urine antigen positive: switched to oral azithromycin, 500 mg daily to complete a 5 day course If both negative: followed empirical treatment.		Incremental (2-1): 0 (CI NR; p = 0.97) **Readmission (mean per patient):** Intvn 1: 0.0225 Intvn 2: 0.0455 Incremental (2-1): 0.0230 (CI NR; p = 0.44) **Adverse events (mean per patient):** Intvn 1: 0.1798 Intvn 2: 0.0909 Incremental (2-1): -0.0889 (CI NR; p = 0.12) **Length of antimicrobial treatment, days (mean per patient):** Intvn 1: 10.5 ± 1.3 Intvn 2: 10.8 ± 1.6 Incremental (2-1): 0.3 (CI NR; p = 0.83) **Length of intravenous treatment, days (mean per patient):** Intvn 1: 5.0 ± 2.6 Intvn 2: 5.2 ± 3.1 Incremental (2-1): 0.2 (CI NR; p = 0.55)	

Data sources
Health outcomes: Health outcomes from within trial. **Quality-of-life weights:** NA. **Cost sources:** Resource use from within trial. Costs taken from Hospital Universitari Arnau de Vilanova.
Comments
Source of funding: CIBERES (Government Funded). **Limitations:** No ICERs were presented; costs are from a single hospital not national list prices; no quality-of-life information provided; patients had to be stable prior to randomisation and as such some costs and outcomes here may not be representative. **Other:** Comparative analysis of outcomes according to therapeutic strategy employed is also provided but is not detailed here. Health outcomes were converted from cohort level to mean per patient by NCGC.
Overall applicability*: Partially applicable **Overall quality**:** Very serious limitations

Abbreviations: b.d = twice daily; CIBERES = Centros de Investigación Biomédica en Red Enfermedades Respiratorias; CCA = cost-consequence analysis; CI = 95% confidence interval; ICER = incremental cost-effectiveness ratio; NR = not reported; t.i.d = three times daily
‡ Converted using 2009 purchasing power parities[7]
** Directly applicable/Partially applicable/Not applicable; ** Minor limitations/Potentially serious limitations/Very serious limitations*

1.4 Antibiotic therapy

Table 2: FREI2005[2]

Frei CR, Burgess DS. Cost-effectiveness of 4 empiric antimicrobial regimens in patients with community-acquired pneumonia. Formulary. 2005; 40(9):298-303				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA (health outcome = per life saved) **Study design:** Retrospective cohort analysis **Approach to analysis:** Analysis of billing data for patients admitted with class IV or V pneumonia **Perspective:** USA hospital **Time horizon:** Length of follow up is unclear, study itself was 6 months long **Treatment effect duration:** N/A **Discounting:** N/A	**Population:** Adults admitted to hospital with either class IV or V pneumonia **Cohort settings:** Start age = 67 - 89 M = 49% N = 311 **Intervention 1:** Levofloxacin (respiratory fluoroquinolone) **Intervention 2:** Ceftriaxone (cephalosporin) **Intervention 3:** Levofloxacin (respiratory fluoroquinolone) plus macrolide **Intervention 4:** Levofloxacin (respiratory fluoroquinolone) plus ceftriaxone (cephalosporin)	**Total costs (mean per patient):** Intvn 1: £2,711 Intvn 2: £2,971 Intvn 3: £3,291 Intvn 4: £3,818 Incremental (2-1): £260 (CI NR; p = NR) Incremental (3-1): £580 (CI NR; p = NR) Incremental (4-3): £527 (CI NR; p = NR) **Currency & cost year:** 2005 US dollars (presented here as 2005 UK pounds‡) **Cost components incorporated:** Hospital billing department: Reparatory therapy, room and board, pharmacy, laboratory, radiology, miscellaneous, central supply and emergency room	**Survival (%):** Intvn 1: 94% Intvn 2: 87% Intvn 3: 98% Intvn 4: 95% Incremental (2-1): -7% (CI NR; p = NR) Incremental (3-1): +4% (CI NR; p = NR) Incremental (4-3): -3% (CI NR; p = NR) **QALYs gained†:** Intvn 1: 5.909 Intvn 2: 5.469 Intvn 3: 6.161 Intvn 4: 5.972 Incremental (2-1): -0.440 (CI NR; p = NR) Incremental (3-1): +0.252 (CI NR; p = NR) Incremental (4-3): -0.189 (CI NR; p = NR)	**ICER (Intvn 2 vs Intvn 1):** Levofloxacin dominates ceftriaxone CI: NR Probability Intvn 2 cost effective (£20K/30K threshold): NR **ICER (Intvn 3 vs Intvn 1):** £12,984 per additional life saved £2,302 per QALY gained† CI: NR Probability Intvn 3 cost-effective (£20K/30K threshold): NR **ICER (Intvn 4 vs Intvn 3):** Ceftriaxone plus levofloxacin dominated by Ceftriaxone plus macrolide CI: NR Probability Intvn 4 cost-effective (£20K/30K threshold): NR **Analysis of uncertainty:** Sensitivity analysis was conducted to vary the mortality rate and total hospital cost. The mortality rate was varied by ± 5% according to a normal distribution, and the total hospital cost was fir to a log-normal distribution and varied over the entire interval.

Data sources				
Health outcomes: Cohort study. Life expectancy from England and Wales life tables[5] **Quality-of-life weights:** average EQ-5D scores for general UK population (70-80 years) from Kind et al (1998)[3] **Cost sources:** Hospital billing department.				
Comments				
Source of funding: Study was support in part by grants from Abbott laboratories and Ortho McNeil Pharmaceuticals. **Limitations:** This is a study from the US which makes it less applicable due to the configuration of their health system; Costs are measured; No quality of life aspects were considered. Information on the doses were not given; Data came from a cohort study that was conducted in a single hospital – not told if it was randomised and the groups were not well matched at baseline; Although the authors use per additional life saved they acknowledge that they were not able to determine deaths that were solely attributable to pneumonia; Hospital charges were used for the costs which is perhaps questionable. A breakdown of these costs and the resource use was not provided; The sensitivity analysis is unlikely to overcome issues with generalisability as the costs are likely to be specific to this particular hospital.				
Overall applicability*: Partially Applicable	**Overall quality**: Very serious limitations**			

Abbreviations: CCA = cost-consequence analysis; CEA = cost-effectiveness analysis; CI = 95% confidence interval; ICER = incremental cost-effectiveness ratio; NA= not applicable; NR = not reported; pa = probabilistic analysis

† QALYs gained and incremental analyses calculated by the NCGC as a complete incremental analysis was not performed in the study. When calculating QALYs gained, these have been discounted by 3.5% per year

‡ Converted using 2011 purchasing power parities [7]

** Directly applicable/Partially applicable/Not applicable; ** Minor limitation/Potentially serious limitations/Very serious limitations*

Table 3: Lloyd 2008[4]

A. Lloyd, A. Holman, and T. Evers. A cost-minimisation analysis comparing moxifloxacin with levofloxacin plus ceftriaxone for the treatment of patients with community-acquired pneumonia in Germany: results from the MOTIV trial. Curr.Med.Res.Opin. 24 (5):1279-1284, 2008.				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: CEA (health outcome: clinical cure)† **Study design:** RCT **Approach to analysis:** resource use from RCT were converted into costs using national sources **Perspective:** Germany hospital (insurer perspective was used in a sensitivity analysis) **Follow-up:** 5 to 7 days after study treatment **Treatment effect duration[(a)]:** up to 7 days after treatment **Discounting:** Costs: NA; Outcomes: NA	**Population:** Subjects with CAP requiring hospitalisation and initial parenteral antibiotic therapy enrolled in the MOTIV trial[8], included in our clinical review. **Patient characteristics:** Intervention 1 N: 368 (all patients were included in the economic analysis [ITT]) Start age: 66 Male: 64% Intervention 2 N: 365 (all patients were included in the economic analysis [ITT]) Start age: 60 Male: 60% **Intervention 1:** Monotherapy respiratory fluoroquinolone: sequential IV and oral moxifloxacin (400 mg once per day). After 3 days of IV therapy patients could be switched to oral therapy at the discretion of the investigator. Duration 7 to 14 days.	**Total costs (mean per patient):** Intervention 1: £1,639 Intervention 2: £1,960 Incremental (2−1): £321 (95% CI £103-£554; p<0.05) **Currency & cost year:** 2006 Euro (presented here as 2006 UK pounds[(b)]) **Cost components incorporated:** Medication, diagnostics, therapeutic procedures, hospitalisation	**Clinical cure (mean per patient):** Intervention 1: 0.796 Intervention 2: 0.838 Incremental (2−1): 0.042 (95% CI NR; p=NR)	**ICER (Intervention 2 versus Intervention 1):** £7,642 per additional clinical cure (pa) 95% CI: Intervention 1 more effective and less costly - £78,721 **Analysis of uncertainty:** When the perspective adopted was that of the insurer, the cost of Intervention 2 was £1,997 and the cost of Intervention 1 was £2,008 (Intervention 2 saves £11).

	Intervention 2: Combination of respiratory fluoroquinolone and cephalosporin: Ceftriaxone (IV 2 g once per day) plus sequential IV and oral levofloxacin (500 mg twice per day). After 3 days of IV therapy with levofloxacin, patients could be switched to oral therapy at the discretion of the investigator. Duration 7 to 14 days.			
Data sources				
Health outcomes: RCT included in our clinical review[8]. **Quality-of-life weights:** NA. **Cost sources:** national sources from Germany.				
Comments				
Source of funding: Bayer Healthcare **Limitations:** Study conducted in Germany from a hospital/insurer perspective. QALYs not estimated. Patients were classified as high severity however mortality in the study was low, suggesting the severity was low. Outcomes obtained from one RCT only the study was sponsored by the manufacturer of the drug given as monotherapy. Adverse events were not assessed which could be an important outcome for fluoroquinolone.				
Overall applicability[(c)]: Partially applicable **Overall quality[(d)]:** Potentially serious limitations				

Abbreviations: CEA: cost-effectiveness analysis; 95% CI: 95% confidence interval; ICER: incremental cost-effectiveness ratio; ITT: intention-to-treat analysis; NR: not reported; QALYs: quality-adjusted life years

(a) For studies where the time horizon is longer than the treatment duration, an assumption needs to be made about the continuation of the study effect. For example, does a difference in utility between groups during treatment continue beyond the end of treatment and if so for how long

(b) Converted using 2006 purchasing power parities[7]

(c) Directly applicable/Partially applicable/Not applicable

(d) Minor limitations/Potentially serious limitations/Very serious limitations

† The study reported the incremental analysis only as a sensitivity analysis as the main conclusion was that there was no statistically significant difference in outcome.

1.4.1 Duration of antibiotic therapy

Table 4: Opmeer 2007[6]

Opmeer BC, el MR, Bossuyt PMM, Speelman P, Prins JM, de borgie CAJM. Costs associated with shorter duration of antibiotic therapy in hospitalized patients with mild-to-moderate-severe community-acquired pneumonia. Journal of Antimicrobial Chemotherapy. 2007; 60(5):1131-1136. *(Guideline Ref ID OPMEER2007)*				
Study details	**Population & interventions**	**Costs**	**Health outcomes**	**Cost effectiveness**
Economic analysis: Cost analysis **Study design:** Within-trial analysis (RCT) of el Moussaoui 2006[1] **Approach to analysis:** Analysis of individual level resource use, using both trial and unit costs **Perspective:** Dutch health care system▫ **Time horizon:** Trial follow up for 28 days **Discounting:** Costs = NA; Outcomes = NA	**Population:** Adults admitted to hospital with mild-to-moderate to severe CAP† **Patient characteristics:** N = 119 Median age = 57.2 M = 59.7% **Intervention 1:** IV amoxicillin for 3 days followed by 750mg PO amoxicillin t.i.d. for 5 days **Intervention 2:** IV amoxicillin for 3 days followed by placebo for 5 days	**Total costs (mean per patient):** Intvn 1: £2,331 Intvn 2: £2,478 Incremental (2-1): -£147 (CI NR; p = NR) **Currency & cost year:** 2002 Euros (presented here as 2002 UK pounds‡) **Cost components incorporated◊:** Hospital admission: Hospital stay Study medications days 1-3 Study medications days 4-8 Other antibiotic therapy Blood gas X-ray thorax Cultures Follow-up: Hospital stay Outpatient specialist consultations	**None**	**Result from health care system perspective:** Incremental (2-1): ICER: NR CI: NA Probability Intvn 2 cost-effective (£20K/30K threshold): NA **Result from societal perspective:** Short course amoxicillin may be cost saving when compared to a standard course Incremental (2-1): ICER: NR CI: -£587 to £847 Probability Intvn 2 cost-effective (£20K/30K threshold): NR **Analysis of uncertainty (societal perspective only):** When undertaken from the societal perspective, short course of amoxicillin is cost saving compared to standard course. 500 repeated bootstrap samples were used to create a 95% CI around the mean difference between short- and standard-course antibiotic therapy. This runs from -£548 to £847. Sensitivity analysis was conducted by varying

		GP visits Company doctor Social services Physiotherapist Psychologist/psychiatrist Other primary care provider		unit costs per day of hospital stay by ±20%. The difference in costs varied between 1.7% and 4.9% in favour of short course therapy. When costs were adjusted to account for increased costs in academic centres, there was a 4.9% increase in mean difference costs in favour of short course antibiotics and total costs substantially decreased.
Data sources				
Health outcomes: None. **Quality-of-life weights:** None. **Cost sources:** Trial data; Dutch national pharmaceutical unit costs; Dutch national reference prices; fees charged and/or compensated by health insurance companies.				
Comments				
Source of funding: Healthcare Insurance Board. **Limitations:** No ICER is presented or can be calculated from the data; only a comparative costing is performed, and as such, no health effects or health-related quality-of-life outcomes are reported; only patients who significantly improve after three days of therapy were randomised into the study; no sensitivity analysis was undertaken on follow-up costs; costs of medication for the placebo group were included after three days, and authors unsure if costs were attributed to placebo; length of follow-up may be inadequate to account for all costs and outcomes. **Other:** There were significantly higher rates of utilisation for outpatient specialist consultation visits and GP visits in the short course arm, leading to higher costs.				
Overall applicability*: Partially applicable **Overall quality**: Very serious limitations**				

Abbreviations: CAP = community acquired pneumonia; CC = Comparative costing; CI = 95% confidence interval; ICER = incremental cost-effectiveness ratio; NR = not reported;
▫ Study used societal perspective but results here have been recalculated to only include health care system costs in line with the NICE reference case
◊ Cost components removed from recalculation due to perspective change include; absence from work (in both hospital admission and follow-up), home care, family care and travel expenses.
†However, only those who made a significant improvement after 72hrs were randomised into the trial. 38 patients were excluded prior to randomisation due to no significant improvement.
‡ Converted using 2002 purchasing power parities [7]
** Directly applicable/Partially applicable/Not applicable; ** Minor limitations/Potentially serious limitations/Very serious limitations*

1.4.2 Timing of antibiotic therapy

No economic evidence was identified.

1.5 Glucocorticosteroid treatment

No economic evidence was identified.

1.6 Gas exchange

No economic evidence was identified.

1.7 Monitoring

No economic evidence was identified.

1.8 Safe discharge

No economic evidence was identified.

1.9 Patient information

No economic evidence was identified.

2. HAP

2.1 Severity assessment

No economic evidence was identified.

2.2 Diagnostic tests

No economic evidence was identified.

2.3 Microbiological tests

No economic evidence was identified.

2.4 Antibiotic therapy

No economic evidence was identified.

2.5 Glucocorticosteroid treatment

No economic evidence was identified.

2.6 Gas exchange

No economic evidence was identified.

2.7 Monitoring

No economic evidence was identified.

2.8 Safe discharge

No economic evidence was identified.

2.9 Patient information

No economic evidence was identified.

3. References

1 el Moussaoui R, de Borgie CAJM, van den Broek P, Hustinx WN, Bresser P, van den Berk GEL et al. Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study. BMJ. 2006; 332(7554):1355

2 Frei CR, Burgess DS. Cost-effectiveness of 4 empiric antimicrobial regimens in patients with community-acquired pneumonia. Formulary. 2005; 40(9):298-303

3 Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. BMJ. 1998; 316(7133):736-741

4 Lloyd A, Holman A, Evers T. A cost-minimisation analysis comparing moxifloxacin with levofloxacin plus ceftriaxone for the treatment of patients with community-acquired pneumonia in Germany: results from the MOTIV trial. Current Medical Research and Opinion. 2008; 24(5):1279-1284

5 Office for National Statistics. Interim life tables, 2009-2011. 2013. Available from: http://www.ons.gov.uk/ons/rel/lifetables/interim-life-tables/2009-2011/index.html [Last accessed: 15 July 2013]

6 Opmeer BC, el MR, Bossuyt PMM, Speelman P, Prins JM, de borgie CAJM. Costs associated with shorter duration of antibiotic therapy in hospitalized patients with mild-to-moderate-severe community-acquired pneumonia. Journal of Antimicrobial Chemotherapy. 2007; 60(5):1131-1136

7 Organisation for Economic Co-operation and Development (OECD). Purchasing power parities (PPP). 2011. Available from: http://www.oecd.org/std/ppp [Last accessed: 16 January 2014]

8 Torres A, Garau J, Arvis P, Carlet J, Choudhri S, Kureishi A et al. Moxifloxacin monotherapy is effective in hospitalized patients with community-acquired pneumonia: the MOTIV study--a randomized clinical trial. Clinical Infectious Diseases. 2008; 46(10):1499-1509