How to choose the duration of antibiotic therapy in patients with pneumonia

Stefano Aliberti[a], *Fabio Giuliani*[b], *Julio Ramirez*[c], *Francesco Blasi*[b], *the DURATION Study Group*

Purpose of review
The appropriate duration of antimicrobial treatment in patients with pneumonia remains a matter of controversy. The purpose of this article is to review different approaches that have been used to determine the duration of antimicrobial therapy mainly driven either by the antibiotic chosen, isolated pathogen, host characteristics, or severity of the disease.

Recent findings
When considered individually, every approach has strengths and weaknesses. Targeting the duration of antibiotic therapy based on a single biomarker, such as procalcitonin, is a promising approach that showed a reduction in antibiotic exposure in different settings, diseases, and study populations. Furthermore, an individualized approach according to time to reach clinical stability takes into account all the previous cited factors and may be another feasible and effective strategy to determine the most appropriate duration of the antibiotic therapy in patients with pneumonia.

Summary
A shorter duration of antibiotic course based on response to treatment may be favorable in patients with pneumonia due to a potential reduction of adverse events and antibiotic resistance, the opportunity to enhance patients' compliance and to decrease healthcare costs.

Keywords
antibiotic, clinical stability, duration of therapy, pneumonia, procalcitonin

INTRODUCTION

One of the crucial targets to reduce morbidity and mortality in patients with pneumonia is to optimize antibiotic usage [1]. During the past decades, increasing evidence has strengthened recommendations of guidelines concerning antibiotic selection, early initiation of therapy, and switch from intravenous to oral therapy [2]. However, the appropriate duration of antimicrobial treatment still remains a matter of controversy.

A shorter duration of antibiotic course may be favorable due to a potential reduction of adverse events and antibiotic resistance, and the opportunity to enhance patients' compliance and to decrease healthcare costs. Nevertheless, these considerations must meet all the criteria for effectiveness of treatment and patients' safety. Most of the recommendations suggested by international guidelines show a weak level of evidence being mostly based on expert opinions rather than results from observational or interventional studies, as recently highlighted (see Table 1) [1,3–5]. Certainly, a point on which experts agree and which is suggested by some guidelines is to individualize duration of antibiotic therapy. However, a significant difference in the duration of therapy is observed depending neither on severity on admission nor patients' response [6]. Conversely, a fixed duration of therapy, ranging from 10 to 14 days in the majority of cases, is detected worldwide, regardless of patients' clinical response (see Fig. 1).

[a]Department of Health Science, University of Milan Bicocca, Clinica Pneumologica, AO San Gerardo, Monza, [b]Department of Pathophysiology and Transplantation, University of Milan, IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy and [c]Division of Infectious Diseases, Department of Medicine, University of Louisville, Louisville, Kentucky, USA

Correspondence to Stefano Aliberti, MD, Department of Health Science, University of Milan Bicocca, Clinica Pneumologica, AO San Gerardo, Via Pergolesi 33, Monza, Italy. Tel: +39 0392339284; mobile: +39 03394171538; fax: +39 0392339437; e-mail: stefano.aliberti@unimib.it

Curr Opin Infect Dis 2015, 28:177–184
DOI:10.1097/QCO.0000000000000140

KEY POINTS

- A short duration of antibiotic course may be favorable in patients with pneumonia due to a potential reduction of adverse events and antibiotic resistance, and the opportunity to enhance patients' compliance and to decrease healthcare costs.
- A comprehensive evaluation of the interaction among host, pathogen, and antibiotic characteristics might be the key to choosing the correct duration of antibiotic therapy in patients with pneumonia.
- Shortening the duration of therapy might follow a biomarker of a favorable response of the immune system to the antibiotic acting on the pathogen causing pneumonia, such as procalcitonin.
- An individualized approach according to time to reach clinical stability may be another feasible and effective strategy to determine the most appropriate duration of the antibiotic therapy in patients with pneumonia.

Different approaches have been used to determine the optimal duration of antimicrobial therapy in patients with pneumonia that are mainly driven either by the antibiotic chosen, isolated pathogen, host characteristics, or severity of the disease.

DURATION OF THERAPY ACCORDING TO THE ANTIBIOTIC CHOSEN

Duration of antibiotic therapy can be chosen according to pharmacokinetic and pharmacodynamic characteristics of the specific antibiotic used. The postantibiotic effect (PAE) is a well defined pharmacodynamic phenomenon that reflects the persistent inhibition of bacterial growth following the removal of an active agent from the culture medium. The clinical significance of PAE pertains primarily to its impact on the dosing schedule of the antimicrobial drug. The most studied antibiotics in terms of PAE include azithromycin, levofloxacin, telithromycin, and beta-lactams [7–15].

Compared to older macrolides, azithromycin is characterized by a prolonged half-life, excellent tissue penetration, and prolonged PAE. Therefore, it is estimated that a significant antibacterial activity against several pathogens might persist in tissue for at least 5 days after a 5-day course of treatment [7]. Several studies compared the efficacy of a 3- versus a 5-day course of azithromycin, showing no differences in the success rate between the two arms [8,9]. Similar results were achieved when azithromycin 500 mg daily for 3 days was compared to a single 1.5 g dose [10]. One of the main advantages of the single dose is represented by its use as a directly observed therapy in patients with low

Table 1. Summary of guideline recommendations for the duration of antibiotic therapy in patients with community-acquired pneumonia

Guideline	Recommended duration	Grade/level of evidence
IDSA/ATS (2007) [4]	Patients with CAP should be treated for a minimum of 5 days (level I evidence*), should be afebrile for 48–72 h, and should have no more than 1 CAP-associated sign of clinical instability before discontinuation of therapy level II evidence*). A longer duration of therapy may be needed if initial therapy was not active against the identified pathogen or if it was complicated by extrapulmonary infection, such as meningitis or endocarditis (level III evidence*).	Level I: high Level II: moderate Level III: low
ERS/ESCMID (2011) [1]	The duration of treatment should generally not exceed 8 days in a responding patient [C2]. Biomarkers, particularly PCT, may guide shorter treatment duration.	C2: Insufficient evidence, from 1 RCT or >1 RCT, but no systematic review or meta-analysis
BTS (2009) [3]	For community managed and for most patients admitted to hospital with low or moderate severity and uncomplicated pneumonia, 7 days of appropriate antibiotics is recommended. For those with high severity microbiologically undefined pneumonia, 7–10 days of treatment is proposed. This may need to be extended to 14 or 21 days according to clinical judgment, for example, where *S. aureus* or Gram-negative enteric bacilli pneumonia is suspected or confirmed. [C].	C: Formal combination of expert views

Table has been reproduced from the original source with permission [5].
ATS, American Thoracic Society; BTS, British Thoracic Society; CAP, community-acquired pneumonia; ERS, European Respiratory Society; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; IDSA, Infectious Diseases Society of America; PCT, procalcitonin; RCT, randomized controlled trial.

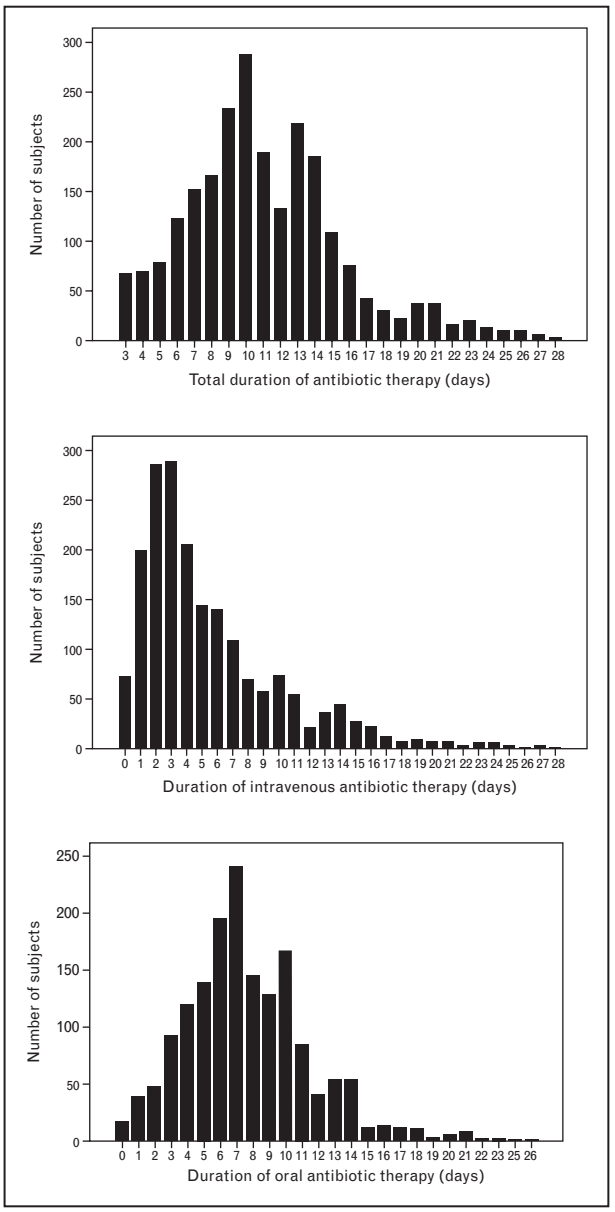

FIGURE 1. Total, intravenous, and oral duration of antibiotic therapy in hospitalized patients with community-acquired pneumonia enrolled in the Community-Acquired Pneumonia Organization database [6].

compliance or in the presence of barriers to filling prescriptions. The administration of a single-dose microsphere formulation of azithromycin was as effective as a 7-day course of levofloxacin or clarithromycin [11,16].

In the field of antibiotics with a PAE, a distinction should be made between two different concepts: duration of administration versus duration of therapy. Although the duration of administration would be shortened because of the PAE, the duration of therapy (as the real effect of the antibiotic) still remains the same. For example, a 3-day course of azithromycin (duration of administration) would correspond to a duration of therapy of 7 days. In view of these considerations, the idea of individualizing duration of therapy in patients with pneumonia according to the antibiotic chosen may have some important limitations.

DURATION OF ANTIBIOTIC THERAPY ACCORDING TO THE IDENTIFIED PATHOGEN

The paradigm of targeting duration of antibiotic treatment in patients with pneumonia according to the isolated pathogen has been extensively applied particularly for atypicals, including *Legionella* spp., as well as *Staphylococcus aureus* and *Pseudomonas aeruginosa* [3,4].

In a large double-blind multicenter study, Dunbar *et al.* [17] compared a 5-day 750 mg levofloxacin regimen to a 10-day 500 mg levofloxacin course for the treatment of pneumonia caused by *Legionella pneumophila*, *Chlamydophila pneumoniae*, or *Mycoplasma pneumoniae*, and no differences in success and relapse rate were shown between the two groups. A randomized controlled trial (RCT) by Yu *et al.* [18] showed that a short course regimen (levofloxacin 750 mg for 5 days) could be effective in the treatment of *L. pneumophila*, while previous recommendations of prolonged therapy (14–21 days) were based on observations involving a large number of immunocompromised patients.

Chastre *et al.* [19] compared an 8-versus a 15-day antibiotic regimen for the treatment of ventilator-associated pneumonia (VAP) showing comparable clinical effectiveness between the two regimens. There was no difference for in-hospital mortality between the two treatment groups in a subpopulation of patients with methicillin-resistant *S. aureus* (MRSA) pneumonia [19]. Mortality rates associated with bacteremic pneumonia were reported to be high in both methicillin-susceptible *S. aureus* (MSSA) (41%) and MRSA (56%) patients [20]. No studies have ever assessed the optimal duration of antibiotic treatment in this specific population. However, expert opinion suggests at least 2 weeks of antibiotic for patients with a *S. aureus* bacteremia mainly because the presence of an unidentified focus of infection outside the blood is still suspected.

Several studies addressed the question of the optimal duration of therapy in pneumonia due to nonfermenting Gram-negative rods (NF-GNRs) with different results [20–23]. In patients with NF-GNR VAP, a short-course treatment was associated with a higher relapse rate than the long-term treatment,

whereas no difference in mortality rate was reported [19]. However, Hedrick *et al.* [24], in their retrospective analysis, showed similar mortality and recurrence rates comparing VAP patients with NF-GNRs treated less and more than 8 days. Finally, when a short course of therapy was used to treat Gram-negative hospital-acquired pneumonia (HAP), relapse rates were significantly higher among patients with NF-GNRs than in patients with other Gram-negative organisms [21].

Duration of therapy tailored to the isolated pathogen may help physicians in de-escalating and shortening the antibiotic treatment, according to the evidence published so far. However, since the causative agent is identified only in a small proportion of patients with pneumonia, this approach cannot be extensively applied in daily clinical practice [3,4].

DURATION OF ANTIBIOTIC THERAPY ACCORDING TO HOST FACTORS

Bacteremia and pneumonia are common complications in neutropenic patients. The Infectious Diseases Society of America (IDSA) guidelines recommend starting empiric antibiotic therapy within 2 h from patient presentation and to continue appropriate treatment until bone marrow recovery or longer if necessary [22]. Pizzo *et al.* [25] compared fixed versus personalized duration of therapy in neutropenic patients with pneumonia. Patients with no fever at day 7 were randomized to either discontinue therapy, regardless of the absolute neutrophil count, or to continue it until the resolution of granulocytopenia. Forty-one percent of patients who discontinued therapy at day 7 experienced recrudescence of fever, suggesting the importance of prolonged antimicrobial treatment in neutropenic patients.

Lower respiratory tract infections (LRTIs) are 25 times more common in patients with HIV than in the general community [26,27]. The British Thoracic Society (BTS) guidelines 2009 do not consider HIV-infected patients and the American Thoracic Society (ATS) guidelines 2007 can be applied to HIV patients whose CD4+ cell count is at least 350/μl [4,6]. In a prospective study performed in Uganda in 1996–1998, Yoshimine *et al.* [28] evaluated the outcome of a 3-day parenteral ampicillin regimen followed by 4–7 days of oral amoxicillin in HIV-negative and HIV-positive patients with community-acquired pneumonia (CAP), with success rates similar in the two groups. Further studies are needed to tackle this issue in patients with profound immunodeficiency (CD4+ <200/μl) in which case opportunistic infections are more likely.

DURATION OF ANTIBIOTIC THERAPY ACCORDING TO SEVERITY OF THE DISEASE

Two meta-analyses evaluated the effectiveness and safety of short versus long-course antibiotic therapy for mild to moderate CAP, involving inpatient and outpatient adults with no need of ICU, and showed no differences in terms of bacteriologic eradication, clinical success, clinical failure, and mortality [29,30]. Few data are available regarding short versus long-course antibiotic regimens in patients with severe CAP. Choudhury *et al.* [31] performed a prospective observational study on CAP patients with a CURB-65 score of 3–5, showing no difference in terms of in-hospital and 30-day outcomes between patients with a short (7 days) versus long-course (>7days) therapy.

To date, there is a lack of data regarding the duration of antibiotic therapy in patients with pneumonia associated with severe sepsis and septic shock or requiring mechanical ventilation. Dellinger *et al.* [32], in the International Guidelines for Management of Severe Sepsis and Septic Shock published in 2008, recommended a duration of antibiotic therapy typically limited to 7–10 days, with a longer course in case of slow clinical response, undrainable foci of infection, or immunologic deficiencies. In the update published in 2013, the authors suggested including bacteremia with *S. aureus* and some fungal and viral infections among the conditions that may require a prolonged course [33].

Although bacteremia may increase mortality in patients with pneumonia, Bordon *et al.* showed, in a retrospective study, that pneumococcal bacteremia seems not to increase mortality in CAP patients and concluded that pneumococcal bacteremia should not be a contraindication for de-escalation of therapy in clinically stable patients [34,35]. A recent meta-analysis by Havey *et al.* [36] including six trials on adult CAP and two trials on adult VAP patients with bloodstream infection evaluated short versus long-course antimicrobial therapy showing no difference in clinical effectiveness between the two groups.

Despite the lack of data, severity assessment is of primary importance in deciding both switch from intravenous to oral and duration of antimicrobial treatment. Most guidelines consider hemodynamic stability and resolution of acute respiratory failure to be the main criteria to switch from intravenous to oral antibiotics (see Table 2) [4,6].

DURATION OF ANTIBIOTIC THERAPY ACCORDING TO LABORATORY BIOMARKERS

A comprehensive evaluation of the interaction among host, pathogen, and antibiotic characteristics might be the key to choosing the correct duration of

Table 2. Criteria for clinical stability and switch from endovenous to oral in patients with community-acquired pneumonia

Reference	Definition	Criteria
ATS 2001 [37]	Criteria for switching to oral antibiotic therapy	Improvement in cough and dyspnea T $\leq$37.8°C on two occasions 8 h apart WBC count decreasing at least 10% Adequate oral intake
ERS/ESCMID 2011 [1]	Criteria for switching to oral antibiotic therapy	Resolution of the most prominent clinical features at admission
ATS/IDSA 2007 [4]	Criteria for clinical stability	T $\leq$37.8°C HR $\leq$100 beats/min RR $\leq$24 breaths/min SBP $\geq$90 mmHg $SatO_2$ $\geq$90% or pO_2 $\geq$60 mmHg Ability to maintain oral intake Normal mental status
BTS 2009 [3]	Features indicating response to initial empirical parenteral therapy permitting consideration of oral antibiotic substitution	Resolution of fever for >24 h HR < 100 beats/min Resolution of tachypnea Clinically hydrated and taking oral fluids Resolution of hypotension Absence of hypoxia Improving white cell count Nonbacteremic infection No microbiological evidence of legionella, staphylococcal or Gram-negative enteric bacilli infection No concerns over gastrointestinal absorption
Halm *et al.* 1998 [38]	Clinical stability	Ability to eat Normal mental status T $\leq$38.3°C HR $\leq$100 beats/min SBP $\leq$90 mmHg RR $\leq$24 breaths/min $SatO_2$ $\geq$90%
van der Eerden *et al.* 2004 [39]	Criteria for switching to oral antibiotics	T < 38°C for 72 h Coughing with or without production of sputum, thoracic pain and dyspnea have improved
Menéndez *et al.* 2004 [40]	Clinical stability	T $\leq$ 37.2°C HR $\leq$ 100 beats/min RR $\leq$ 24 breaths/min SBP $\geq$ 90 mmHg SpO_2 $\geq$ 90% or PaO_2 $\geq$ 60 mmHg when the patient is not receiving supplemental oxygen. In patients with home oxygen therapy stability is considered when their oxygen need is the same as prior to admission
Shindo *et al.* 2008 [41]	Criteria for switching to oral antibiotics	T $\leq$37.8°C for 16 h WBC decreasing (WBC $\leq$ 10 000/mm^3) Adequate oral intake Improvement in cough and dyspnea

ATS, American Thoracic Society; BTS, British Thoracic Society; CAP, community-acquired pneumonia; CRP, C-reactive protein; ERS, European Respiratory Society; ESCMID, European Society of Clinical Microbiology and Infectious Diseases; HR, heart rate; IDSA, Infectious Diseases Society of America; PaO_2, partial pressure of oxygen in arterial blood; PCT, procalcitonin; RCT, randomized controlled trial; RR, respiratory rate; $SatO_2$, oxygen saturation; T, temperature; WBC, white blood cells.

antibiotic therapy in patients with pneumonia (see Fig. 2). Ideally, shortening the duration of therapy should follow a marker of a favorable response of the immune system to the antibiotic acting on the pathogen causing pneumonia. The first patient response that could be appreciated in daily clinical practice is a reduction of systemic inflammation by an improvement of biomarkers.

Recently, several biomarkers of inflammation/infection have been tested in patients with pneumonia and, among them, procalcitonin (PCT) seems to be the most promising [42–45]. A recent meta-

analysis included 14 RCTs with a total of 4221 patients with acute respiratory tract infections assigned to receive antibiotics based on a PCT-guided algorithm versus usual care [44]. PCT-guided strategy was confirmed to lead to lower antibiotic exposure, and when considering CAP and VAP independently, similar results were reported. Albrich *et al.* [43] performed an international observational quality surveillance on 1759 patients with a diagnosis of LRTI. Every participant center was provided with a published PCT algorithm for antibiotic guidance. Antibiotic duration was significantly shorter if the PCT algorithm was followed compared with when it was overruled. No increased risk of adverse outcomes was associated with holding the antibiotic therapy on admission or ceasing it early when the decision was guided by the PCT algorithm.

According to recent evidence on the use of biomarkers, a marked reduction in antibiotic exposure has been detected in all different settings, diseases, and study populations. However, one of the biggest concerns is that all the studies used PCT and no other biomarker-oriented approaches in discontinuing antibiotic therapy in LRTI. Furthermore, most of the studies came from Europe, especially Switzerland, which may not reflect the broader experience, and PCT threshold varies significantly from study to study. The PCT-guided algorithms were very heterogeneous, as well as the values of PCT cut-offs chosen to make therapeutic decisions. Finally, severely immunocompromised and neutropenic patients were mostly excluded from RCTs and this could preclude the generalizability of the results. Major limitations to the implementation of a biomarker-based approach in clinical practice are the availability and cost of these biomarkers that mainly depend on the site of care and the resources available.

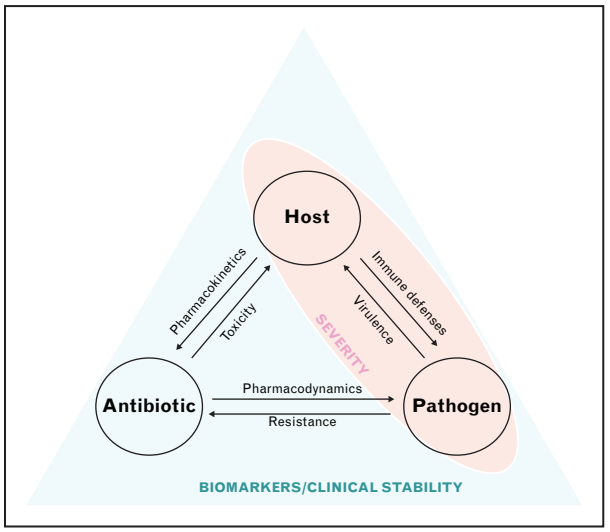

FIGURE 2. Interaction among host, pathogen, and antibiotic characteristics in patients with pneumonia.

INDIVIDUALIZING DURATION OF ANTIBIOTIC THERAPY ACCORDING TO PATIENTS' CLINICAL RESPONSE

Outside of the ICU where patients with pneumonia are intubated and cannot interact with their treating physicians, patients' response to antibiotics could be easily evaluated according to their signs and symptoms. One of the first and most important clinical outcomes in patients with pneumonia is the time in which they reach clinical stability. Several criteria of clinical stability have been suggested, including an improvement of patient symptoms, signs of systemic response, vital parameters, and oxygenation (see Table 2) [46]. Clinical stability criteria have been proven to be useful in guiding the switch of antibiotic therapy from intravenous to oral formulations, and we could speculate that clinical stability criteria could also be useful to decide the duration of antimicrobial treatment [47].

Recently, an international, noninferiority, pragmatic RCT has been designed in patients hospitalized due to CAP to assess the efficacy of an individualized approach to the duration of antibiotic therapy: a treatment duration based on each patient's clinical response compared to local standard approach (clinical trial: NCT01492387). The 'Duration trial' is currently ongoing and so far no significant difference has been shown between the two study groups regarding 30-day clinical outcomes.

CONCLUSION

A prolonged exposure to antibiotics may encourage the development of acquisition of antibiotic-resistant organisms and may be associated with serious adverse reactions. The need to move towards an individualized approach to duration of therapy in pneumonia should be emphasized. The individualized approach in determining the duration of antibiotic therapy in CAP patients is still a recommendation based only on expert opinion. Future research in this area should include prospective, randomized, clinical trials enrolling patients who receive antibiotics using the current standard approach versus an individualized strategy based on the patients' clinical response.

Acknowledgements

Members of the DURATION Study Group are: Bonaiti Giulia, MD, Faverio Paola, MD (Health Science Department, University of Milan Bicocca, Milan, Italy);

Carugati Manuela, MD (University of Milan, Milan, Italy), Spoletini Giulia, MD (Department of Pathophysiology and Transplantation, University of Milan, IRCCS Fondazione Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy), Fantini Riccardo, MD (University of Modena Reggio Emilia), Tedeschi Sara, MD (University of Bologna), Milani Giuseppe, MD (Sant'Anna Hospital, Como, Italy), Villani Massimiliano, MD (Ospedale San Carlo, Milano, Italy), Del Forno Manuela, MD (University of Bologna, Bologna, Italy), Piro Roberto, MD (Arcispedale S. Maria Nuova, Reggio Emilia, Italy), Deotto Martina, MD (AO Sanata Maria della Misericordia, Udine, Italy), Pancini Lisa, MD (University of Milan, IRCCS San Donato, San Donato Milanese, Italy), Voza Antonio, MD (ICH, Rozzano, Italy).

Financial support and sponsorship

No financial support/sponsorship has been requested for this manuscript.

Conflicts of interest

Outside of the submitted work, A.S. had relationship with Astrazeneca (consultancy), B.F. with Almirall, Munipharma, GSK, Menarini, Guidotti-Malesci, Novartis (board membership); GSK and Menarini (consultancy); Pfizer, Zambon, Chiesi (grants), Astrazeneca, Novartis, Pfizer, Almirall, Menarini, Guidotti-Malesci, Chiesi, GSK, Zambon (lectures).

REFERENCES

1. Woodhead M, Blasi F, Ewig S, *et al.* Guidelines for the management of adult lower respiratory tract infections: full version. Clin Microbiol Infect 2011; 17 (Suppl 6):E1–59.
2. Ramirez JA, Vargas S, Ritter GW, *et al.* Early switch from intravenous to oral antibiotics and early hospital discharge: a prospective observational study of 200 consecutive patients with community-acquired pneumonia. Arch Intern Med 1999; 159:2449–2454.
3. Lim WS, Baudouin SV, George RC, *et al.* BTS guidelines for the management of community acquired pneumonia in adults: update. Thorax 2009; 64 (Suppl 3):iii1–iii55.
4. Mandell LA, Wunderink RG, Anzueto A, *et al.* Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis 2007; 44 (Suppl 2):S27–72.
5. Pinzone MR, Cacopardo B, Abbo L, Nunnari G. Duration of antimicrobial therapy in community acquired pneumonia: less is more. ScientificWorldJournal 2014; 2014:759138.
6. Aliberti S, Blasi F, Zanaboni AM, *et al.* Duration of antibiotic therapy in hospitalised patients with community-acquired pneumonia. Eur Respir J 2010; 36:128–134.
7. Schentag JJ, Ballow CH. Tissue-directed pharmacokinetics. Am J Med 1991; 91:5S–11S.
8. Schönwald S, Skerk V, Petricevic I, *et al.* Comparison of three-day and five-day courses of azithromycin in the treatment of atypical pneumonia. Eur J Clin Microbiol Infect Dis 1991; 10:877–880.
9. Socan M. Treatment of atypical pneumonia with azithromycin: comparison of a 5-day and a 3-day course. J Chemother 1998; 10:64–68.
10. Schönwald S, Kuzman I, Oreskovic K, *et al.* Azithromycin: single 1.5 g dose in the treatment of patients with atypical pneumonia syndrome: a randomized study. Infection 1999; 27:198–202.
11. D'Ignazio J, Camere MA, Lewis DE, *et al.* Novel, single-dose microsphere formulation of azithromycin versus 7-day levofloxacin therapy for treatment of mild to moderate community-acquired pneumonia in adults. Antimicrob Agents Chemother 2005; 49:4035–4041.
12. Shorr AF, Zadeikis N, Xiang JX, *et al.* A multicenter, randomized, double-blind, retrospective comparison of 5- and 10-day regimens of levofloxacin in a subgroup of patients aged > or = 65 years with community-acquired pneumonia. Clin Ther 2005; 27:1251–1259.
13. Tellier G, Niederman MS, Nusrat R, *et al.* Clinical and bacteriological efficacy and safety of 5 and 7 day regimens of telithromycin once daily compared with a 10 day regimen of clarithromycin twice daily in patients with mild to moderate community-acquired pneumonia. J Antimicrob Chemother 2004; 54:515–523.
14. Hanberger H, Nilsson LE, Nilsson M, *et al.* Postantibiotic effect of beta-lactam antibiotics on gram-negative bacteria in relation to morphology, initial killing and MIC. Eur J Clin Microbiol Infect Dis 1991; 10:927–934.
15. El Moussaoui R, de Borgie CAJM, van den Broek P, *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. Br Med J 2006; 332:1355.
16. Drehobl MA, De Salvo MC, Lewis DE, Breen JD. Single-dose azithromycin microspheres vs. clarithromycin extended release for the treatment of mild-to-moderate community-acquired pneumonia in adults. Chest 2005; 128:2230–2237.
17. Dunbar LM, Khashab MM, Kahn JB, *et al.* Efficacy of 750-mg, 5-day levofloxacin in the treatment of community-acquired pneumonia caused by atypical pathogens. Curr Med Res Opin 2004; 20:555–563.
18. Yu VL, Greenberg RN, Zadeikis N, *et al.* Levofloxacin efficacy in the treatment of community-acquired legionellosis. Chest 2004; 125:2135–2139.
19. Chastre J, Wolff M, Fagon J-Y, *et al.* Comparison of 8 vs. 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. J Am Med Assoc 2003; 290:2588–2598.
20. González C, Rubio M, Romero-Vivas J, *et al.* Bacteremic pneumonia due to *Staphylococcus aureus*: a comparison of disease caused by methicillin-resistant and methicillin-susceptible organisms. Clin Infect Dis 1999; 29:1171–1177.
21. Pugh RJ, Cooke RPD, Dempsey G. Short course antibiotic therapy for Gram-negative hospital-acquired pneumonia in the critically ill. J Hosp Infect 2010; 74:337–343.
22. Freifeld AG, Bow EJ, Sepkowitz KA, *et al.* Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. Clin Infect Dis 2011; 52:e56–e93.
23. Nseir S, Deplanque X, Di Pompeo C, *et al.* Risk factors for relapse of ventilator-associated pneumonia related to nonfermenting Gram negative bacilli: a case-control study. J Infect 2008; 56:319–325.
24. Hedrick TL, McElearney ST, Smith RL, *et al.* Duration of antibiotic therapy for ventilator-associated pneumonia caused by nonfermentative gram-negative bacilli. Surg Infect 2007; 8:589–597.
25. Pizzo PA, Robichaud KJ, Gill FA, *et al.* Duration of empiric antibiotic therapy in granulocytopenic patients with cancer. Am J Med 1979; 67:194–200.
26. Benito N, Moreno A, Miro JM, *et al.* Pulmonary infections in HIV-infected patients: an update in the 21st century. Eur Respir J 2012; 39:730–745.
27. Feikin DR, Feldman C, Schuchat A, Janoff EN. Global strategies to prevent bacterial pneumonia in adults with HIV disease. Lancet Infect Dis 2004; 4:445–455.
28. Yoshimine H, Oishi K, Mubiru F, *et al.* Community-acquired pneumonia in Ugandan adults: short-term parenteral ampicillin therapy for bacterial pneumonia. Am J Trop Med Hyg 2001; 64 (3–4):172–177.
29. Dimopoulos G, Matthaiou DK, Karageorgopoulos DE, *et al.* Short- versus long-course antibacterial therapy for community-acquired pneumonia: a meta-analysis. Drugs 2008; 68:1841–1854.
30. Li JZ, Winston LG, Moore DH, *et al.* Efficacy of short-course antibiotic regimens for community-acquired pneumonia: a meta-analysis. Am J Med 2007; 120:783–790.
31. Choudhury G, Mandal P, Singanayagam A, *et al.* Seven-day antibiotic courses have similar efficacy to prolonged courses in severe community-acquired pneumonia: a propensity-adjusted analysis. Clin Microbiol Infect 2011; 17:1852–1858.
32. Dellinger RP, Levy MM, Carlet JM, *et al.* Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock. Intensive Care Med 2008; 34:17–60.
33. Dellinger RP, Levy MM, Rhodes A, *et al.* Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock. Intensive Care Med 2013; 39:165–228.
34. Agbaht K, Diaz E, Muñoz E, *et al.* Bacteremia in patients with ventilator-associated pneumonia is associated with increased mortality: a study comparing bacteremic vs. nonbacteremic ventilator-associated pneumonia. Crit Care Med 2007; 35:2064–2070.
35. Bordón J, Peyrani P, Brock GN, *et al.* The presence of pneumococcal bacteremia does not influence clinical outcomes in patients with community-acquired pneumonia: results from the Community-Acquired Pneumonia Organization (CAPO) International Cohort study. Chest 2008; 133:618–624.
36. Havey TC, Fowler RA, Daneman N. Duration of antibiotic therapy for bacteremia: a systematic review and meta-analysis. Crit Care 2011; 15:R267.
37. American Thoracic Society. Guidelines for the management of adults with community-acquired pneumonia. Am J Respir Crit Care Med 2001; 163: 1730–624.

38. Halm EA, Fine MJ, Marrie TJ, *et al.* Time to clinical stability in patients hospitalized with community-acquired pneumonia: implications for practice guidelines. J Am Med Assoc 1998; 279:1452–1457.
39. van der Eerden MM, de Graff CS, Vlaspolder F, *et al.* Evaluation of an algorithm for switching from IV to PO therapy in clinical practice in patients with community-acquired pneumonia. Clin Ther 2004; 26:294–303.
40. Menéndez R, Torres A, Rodríguez de Castro F, *et al.* Reaching stability in community-acquired pneumonia: the effects of the severity of disease, treatment, and the characteristics of patients. Clin Infect Dis 2004; 39:1783–1790.
41. Shindo Y, Sato S, Maruyama E, *et al.* Implication of clinical pathway care for community-acquired pneumonia in a community hospital: early switch from an intravenous beta-lactam plus a macrolide to an oral respiratory fluoroquinolone. Intern Med 2008; 47:1865–1874.
42. Christ-Crain M, Stolz D, Bingisser R, *et al.* Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. Am J Respir Crit Care Med 2006; 174:84–93.
43. Albrich WC, Dusemund F, Bucher B, *et al.* Effectiveness and safety of procalcitonin-guided antibiotic therapy in lower respiratory tract infections in 'real life': an international, multicenter poststudy survey (ProREAL). Arch Intern Med 2012; 172:715–722.
44. Schuetz P, Müller B, Christ-Crain M, *et al.* Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. Cochrane Database Syst Rev Online 2012; 9:CD007498.
45. Schuetz P, Litke A, Albrich WC, *et al.* Blood biomarkers for personalized treatment and patient management decisions in community-acquired pneumonia. Curr Opin Infect Dis 2013; 26:159–167.
46. Aliberti S, Zanaboni AM, Wiemken T, *et al.* Criteria for clinical stability in hospitalised patients with community-acquired pneumonia. Eur Respir J 2013; 42:742–749.
47. Ramirez JA, Bordon J. Early switch from intravenous to oral antibiotics in hospitalized patients with bacteremic community-acquired *Streptococcus pneumoniae* pneumonia. Arch Intern Med 2001; 161:848–850.