Medical treatment of pleural infection: antibiotic duration and corticosteroid usefulness

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Shareable abstract (@ERSpublications)
Short antibiotic courses may be non-inferior to longer ones in community-acquired pleural infection that does not require surgery. Corticosteroids offer no benefit in patients with community-acquired pneumonia and pleural effusion. https://bit.ly/3ZQKycY

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Abstract

The data about the optimal duration of antibiotics and the usefulness of corticosteroids in the management of parapneumonic effusion and pleural infection are scarce. Two randomised controlled trials evaluating short antibiotic courses (ODAPE and SLIM) and another trial assessing the benefit from corticosteroid use (STOPPE) in this setting were recently published. The aim of this journal club is to present these trials and discuss their significance and limitations. ODAPE compared the efficacy and safety of a short (2 weeks) *versus* an extended (3 weeks) course of amoxicillin–clavulanate in community-acquired complicated parapneumonic effusions, while SLIM compared the efficacy and safety of short (14–21 days) *versus* longer (28–42 days) antibiotic courses in patients with community- or hospital-acquired pleural infection. STOPPE assessed the benefit from dexamethasone use in patients with community-acquired pneumonia and concomitant pleural effusion. Both ODAPE and SLIM found that shorter antibiotic courses produce less adverse events while being equally efficacious to the longer courses in a subgroup of patients, such as those with pleural infection that is stabilised with only medical treatment and does not require surgery. In contrast, STOPPE found no benefit from the use of dexamethasone in unselected patients with pneumonia and pleural effusion. Due to the significant limitations of these trials, further studies are required to confirm these findings.

Commentary on:

- Hassan M, *et al*. The Short *versus* Long Antibiotic Course for Pleural Infection Management (SLIM) randomised controlled open-label trial. *ERJ Open Res* 2023; 9: 00635-2022.
- Porcel JM, *et al*. Two *vs*. three weeks of treatment with amoxicillin–clavulanate for stabilized community-acquired complicated parapneumonic effusions. A preliminary non-inferiority, double-blind, randomized, controlled trial. *Pleura Peritoneum* 2020; 5: 20190027.
- Fitzgerald DB, *et al*. Steroid Therapy and Outcome of Parapneumonic Pleural Effusions (STOPPE): a pilot randomized clinical trial. *Am J Respir Crit Care Med* 2022; 205: 1093–1101.

Context

Pleural infection represents the invasion of the pleura by bacteria that usually reach the pleural space by translocation from the adjacent lung parenchyma in patients with pneumonia and less frequently through other events (*e.g.* surgical procedures, thoracic trauma, thoracentesis, subdiaphragmatic infections) [1, 2]. Although pneumonia is accompanied by parapneumonic effusion (PPE) in up to 50% of the cases, only 15% of them are complicated by pleural infection (*i.e.* complicated parapneumonic effusion (CPPE)) [1, 3].

Regardless of the causing mechanism, pleural infection is characterised by an intense inflammatory response leading to the formation of pleural adhesions and loculations as well as to the development of empyema [3, 4]. Contrary to the uncomplicated (or simple) PPEs, which usually resolve with only antibiotics, pleural infection requires prompt drainage of the infected pleural fluid with a small-bore chest tube, along with appropriate medical treatment, mainly consisting of antibiotics, nutritional support and thromboprophylaxis [3, 5]. Approximately 15–20% of patients require surgical removal of the infected fluid due to failure of medical treatment [3].

Regarding antibiotics, the questions upon diagnosis of pleural infection are "which antibiotics" to use and "for how long". Since the initial antibiotic regimen is usually empiric, a key role in choosing the antibiotics is played by the bacteriology of pleural infection, which has been found to be different from that of pneumonia and to depend on the source of infection (community- *versus* hospital-acquired) [3, 6–8]. In contrast, data about the optimal length of the antibiotic course are scarce. Until recently, no randomised controlled trial (RCT) had ever assessed the appropriate duration of antibiotics in pleural infection, and therefore, an antibiotic course of at least 3 weeks was usually administered, based on extrapolation of data for the treatment of lung abscess [3]. This is why the publication of two recent trials (Optimal Duration of Antibiotics in Parapneumonic Effusions (ODAPE) and Short *versus* Long antibiotic course for pleural Infection Management (SLIM)) evaluating the efficacy of shorter antibiotic courses in pleural infection has gathered great interest [9, 10]. Regarding medical treatment beyond antibiotics, the intense pleural inflammation that characterises pleural infection has raised the hypothesis of a possible benefit from the use of anti-inflammatory drugs. Due to the absolute lack of evidence on this issue, significant attention has been given to the recent publication of the Steroid Therapy and Outcome of Parapneumonic Pleural Effusions (STOPPE) trial, which evaluated corticosteroids in the treatment of PPEs [11].

The aim of this journal club is to describe the methods and results of the ODAPE, SLIM and STOPPE trials, and discuss their significance and limitations.

Methods

ODAPE trial

ODAPE was a randomised, double-blind, non-inferiority trial that aimed to compare the efficacy and safety of a short (2 weeks) *versus* an extended (3 weeks) course of amoxicillin–clavulanate in CPPEs [10]. Adults with community-acquired pneumonia and an associated pleural effusion meeting the criteria for CPPE were eligible only if they achieved "clinical stability" after 2 weeks of amoxicillin–clavulanate. Enrolled patients were randomly assigned to placebo or amoxicillin–clavulanate for an additional week. The primary purpose was to compare the rate of "clinical success" at 1 week from randomisation between the groups, while secondary outcomes included the rate of pleural thickening >10 mm at 12 weeks and the incidence of antibiotic-related adverse events. Monitoring visits were scheduled at days 1 (eligibility), 14 (randomisation), 21 (primary end-point and adverse events), and 90 (primary end-point and residual pleural thickening) from antibiotic initiation. The criteria for CPPE, "clinical stability", and "clinical success" or "clinical failure" are shown in table 1. Based on a power analysis aiming for statistical power of 80% with a primary outcome event of 90% and a non-inferiority margin of 10% between the groups, it was estimated that 284 patients should undergo randomisation.

SLIM trial

SLIM was an open label, RCT of adults with pleural infection that aimed to compare the efficacy and safety of a short antibiotic course to those of a long antibiotic course [9]. Eligibility required hospital admission due to community- or hospital-acquired pleural infection, low-to-intermediate RAPID (renal, age, purulence, infection source, dietary factors) score (*i.e.* 0–4) at admission, and the potential for discharge within 14 days. Participants were randomised to either a short (14–21 days) or a long (28–42 days) antibiotic course that was administered intravenously during their hospitalisation and continued orally after discharge, for a minimum of 7 and 14 days up to a maximum of 21 and 42 days, respectively. The initial antibiotic regimen was based on guidelines and local patterns of bacterial resistance, whereas subsequent modifications were allowed according to pleural fluid culture results (if positive). Patient recovery and adherence to treatment were evaluated by follow-up visits at 2 and 6 weeks post-discharge. The primary aim was to assess the difference in the incidence of "treatment failure" within 6 weeks from admission between the groups. The secondary purpose was to compare the total duration of antibiotics, the proportion of patients with normal activity within 6 weeks from admission, the time from discharge to achieving normal activity, and the incidence of antibiotic-related adverse events between the groups. Finally, a *post hoc* analysis was performed to assess the difference in the rate of residual pleural effusion and persistent respiratory symptoms at 6 weeks from admission. The criteria used to define pleural infection and treatment failure are shown in table 1.

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TABLE 1 Main characteristics of the studies

	ODAPE	SLIM	STOPPE
Study period	2015–2019	2020–2021	2018–2020
Inclusion criteria	Age ⩾18 years Community-acquired CPPE Clinical stability after 2 weeks of amoxicillin–clavulanate (*i.v.* 2000/200 mg three times daily switched to 875/125 mg three times daily orally when afebrile with normal vital signs and descending CRP levels)	Age ⩾18 years Pleural infection (community- or hospital-acquired) Low–intermediate (0–4) RAPID score at admission Fit for discharge within 14 days	Age ⩾18 years CAP and pleural effusion at or within 72 h from hospital admission
Definitions	CPPE (at least one): Large effusion (⩾50% hemithorax) Loculated effusion Purulent fluid Pleural fluid pH ⩽7.20 Glucose <60 mg·dL^{-1} Bacteria on pleural fluid stains/cultures Clinical stability (all criteria): Temperature <37.8°C Resting pulse rate <100 per min Respiratory rate <24 breaths·min^{-1} Systolic blood pressure >90 mmHg for the last 48 h Pleural effusion occupying <20% of hemithorax on chest radiography >50% reduction in baseline serum CRP Absence of chest drain (already removed)	Pleural infection (at least one): Pus in pleural cavity Positive pleural fluid Gram stain or culture Pleural fluid pH <7.20 Pleural fluid glucose <40 mg·dL^{-1}	Clinical stability: Discharge home OR all the following: Afebrile Systolic pressure >90 mmHg Oxygen saturation >95% on room air Heart rate <100 beats·min^{-1} Respiratory rate <20 breaths·min^{-1} for at least 12 h
Exclusion criteria	Pregnancy Allergy to co-amoxiclav Active TB HAP or HCAP Immunosuppression Non-parapneumonic empyema Life expectancy <3 months Isolation of bacteria resistant to co-amoxiclav	Recurrent ipsilateral pleural infection within past 3 months Pleural effusion that could not be drained at diagnosis Large residual effusion despite drainage Surgery during admission	Need for ICU care Acute burns Recent gastrointestinal bleeding Adrenal insufficiency Steroids for other indications Long-term steroid use Acute delirium Prior steroid-induced psychosis Severe immunodeficiency Cystic fibrosis Active TB Pregnancy/lactation Non-reversible bleeding diathesis Poorly controlled diabetes Blood glucose >20 mmol·L^{-1} at screening Inability to consent
Treatment arms	1) Placebo 2) Amoxicillin–clavulanate for 1 week	1) Short (14–21 days) antibiotic course 2) Long (28–42 days) antibiotic course	1) Dexamethasone *i.v.* (4 mg twice daily for 48 h) 2) Placebo
Randomisation	1:1 ratio	1:1 ratio	2:1 ratio

Continued

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TABLE 1 Continued

	ODAPE	SLIM	STOPPE
Primary outcome	"Clinical success" at 1 week from randomisation "Clinical success" defined as resolution of infection symptoms and signs with no recurrence during follow-up "Clinical failure" defined as persistence or recurrence of infection symptoms and signs, need for further pleural procedures or death due to sepsis	"Treatment failure" within 6 weeks post-admission "Treatment failure" defined as symptom worsening or recurrence with either biochemical (*i.e.* increase in leukocyte or CRP levels) or radiological (*i.e.* new or increasing pleural effusion) indices of uncontrolled pleural infection	
Secondary or exploratory outcomes	Pleural thickening >10 mm at 12 weeks from antibiotic initiation Antibiotic-related adverse events	Total duration of antibiotic treatment Patients with normal activity within 6 weeks post-admission Time from discharge to achieving normal activity Antibiotic-related adverse events Residual pleural effusion and persistent respiratory symptoms 6 weeks post-admission (*post hoc*)	Time to overall clinical stability Use of pleural interventions (*e.g.* therapeutic aspiration >200 mL, thoracostomy or intrapleural fibrinolytics) Incidence of adverse events Duration of antibiotic treatment Duration of hospitalisation Levels of inflammatory markers Size of effusion

ODAPE: Optimal Duration of Antibiotics in Parapneumonic Effusions; SLIM: Short *versus* Long antibiotic course for pleural Infection Management; STOPPE: Steroid Therapy and Outcome of Parapneumonic Pleural Effusions; RAPID score: renal, age, purulence, infection source, dietary factors; CRP: C-reactive protein; CAP: community-acquired pneumonia; CPPE: complicated parapneumonic effusion; co-amoxiclav: amoxicillin–clavulanate; TB: tuberculosis; HAP: hospital-acquired pneumonia; HCAP: health-care associated pneumonia; ICU: intensive care unit.

STOPPE trial

STOPPE was a randomised placebo-controlled multicentre trial that aimed to evaluate corticosteroids in the management of PPEs [11]. Hospitalised adults with community-acquired pneumonia and pleural effusion at or within 72 h from hospital admission were randomised to intravenous dexamethasone or placebo along with standard clinical care. Patients were followed for 30 days with clinical (every alternate day during hospitalisation and at days 14 and 30) and laboratory (chest radiography, leukocyte count and C-reactive protein (CRP) at days 1, 3, 14 and 30) evaluation as well as with the Short Form Health Survey questionnaire (at baseline, discharge and day 30). All data were analysed on an intention-to-treat basis. Given that STOPPE was a pilot study, the purpose was not to set predefined end-points but to capture clinically relevant outcomes (table 1).

Results

The characteristics of the included patients and the results of the studies are shown in tables 2 and 3.

ODAPE trial

ODAPE was terminated early due to a slow enrolment rate caused by the strict eligibility criteria and the absolute lack of recruitment from four out of the six participating medical centres. Moreover, 77% (183 out of 238) of the patients recruited by the remaining centres were finally excluded due to protocol deviation (*i.e.* antibiotics other than amoxicillin–clavulanate), non-parapneumonic cause of pleural infection, presence of cancer or other immunosuppressive states, and lack of clinical stability after 2 weeks of treatment. Despite the premature termination, approval from the local research committee was received to compare the rate of clinical success between the groups, accepting that the non-inferiority hypothesis would be proven if the 95% confidence interval upper bound of the difference in clinical success rate was <10%. Of the 55 included patients, 25 were allocated to the short and 30 to the extended antibiotic regimen. Patient characteristics and their adherence to oral antibiotic treatment (optimal in both groups) were balanced between the groups. Clinical success was achieved in 100% and 97% (difference: 3%, 95% CI −3–9.7%) of patients in the short- and the extended-regimen group, respectively. The patient with clinical failure from the extended-regimen group had an enlarged pleural effusion that required therapeutic thoracentesis and antibiotics for two more weeks. The 95% confidence interval upper bound of the 3% difference between the groups was below 10% suggesting that the 2-week regimen was non-inferior to the 3-week regimen. Moreover, no significant difference was found in the rate of antibiotic-related adverse events between the groups, although oral candidiasis and diarrhoea was reported in two patients from the extended-regimen group. Due to loss of four patients from the extended-regimen group during follow-up

TABLE 2 Patient characteristics

	ODAPE		SLIM		STOPPE	
	2-week course	3-week course	Short course	Long course	Dexamethasone	Placebo
Patients, n	25	30	25	25	51	28
Age, years	60 (50–75)	58 (49–67)	43 (34–49)	52 (39–59)	61.6±17.7	66.7±18.2
Male	76%	83%	72%	68%	39%	36%
Infection source						
Community	25 (100%)	30 (100%)	20 (80%)	22 (88%)	51 (100%)	28 (100%)
Hospital	0 (0%)	0 (0%)	5 (20%)	3 (12%)	0 (0%)	0 (0%)
RAPID score						
Low	8%	13%	68%	40%		
Medium	60%	77%	32%	60%		
High	32%	10%				
Loculations	100%	97%	29%	78%	33%	32%
WBC, $\times10^9$ cells per L	14.5 (10.3–19.1)	16.2 (13.2–19.9)	12.3 (8.77–17.23)	12.8 (10.2–18.85)	14.3±7.3	13.7±7.6
Serum CRP, mg·dL^{-1}	285 (220–374)	270 (196–335)	158.7±94.9	163.6±92.6	240.8±123.3	191.2±119.1
Effusion sampled	25 (100%)	30 (100%)	25 (100%)	25 (100%)	25 (49%)	12 (43%)
Exudate					20 (80%)	9 (75%)
pH of pleural fluid	7.12 (6.8–7.27)	7.0 (6.99–7.24)			7.27±0.26	7.16±0.29
LDH in pleural fluid, IU·L^{-1}					656 (246–1930)	973 (274–2422)

Data are presented as number (%), mean±SD or median (interquartile range) as presented in the original studies, unless stated otherwise. ODAPE: Optimal Duration of Antibiotics in Parapneumonic Effusions; SLIM: Short *versus* Long antibiotic course for pleural Infection Management; STOPPE: Steroid Therapy and Outcome of Parapneumonic Pleural Effusions; RAPID score: renal, age, purulence, infection source, dietary factors; WBC: white blood cells; CRP: C-reactive protein; LDH: lactate dehydrogenase.

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TABLE 3 Study outcomes

	ODAPE		SLIM		STOPPE[#]	
	2-week course	3-week course	Short course	Long course	Dexamethasone	Placebo
Patients, n	25	30	25	25	51	28
Primary outcome	Clinical success at 1 week post-randomisation		Treatment failure by 6 weeks post-admission		Overall time to clinical stability, h	
	100% (n=25) (95% CI 86–100%)	97% (n=29) (95% CI 83–100%) (p=0.36, difference: 3%, 95% CI −3–9.7%)	16.7%	12.5%	41 (95% CI 32.3–54.5)	27.8 (95% CI 15.4–49.5)
Secondary/exploratory outcomes						
Duration of *i.v.* antibiotics, days	6 (4.5–7)	5 (4–7)	9.12±3.56	11.2±2.51	11.0±8.4	8.9±8.2
Duration of total antibiotic treatment, days	14	21	20.5 (18–22.5)	34.5 (32–38)*	22.4±15.4	20.4±13.8
Length of hospital stay, days	7 (5–8)	6.5 (5–9)	10.52±3.28	11.63±2.58	6.0 (5–10)	5.5 (5–8)
Adverse events	0%	7% (difference: −7%, 95% CI −16–2%; non-inferior)	0%	8.3%	49%	35.7%
Chest drain	100%	100%	100%	100%	49%	42.9%
Intrapleural fibrinolytics	92%	100%	N/A	N/A	29.4%	17.9%
Residual pleural findings	Pleural thickening >10 mm at day 90		Pleural effusion at 6 weeks		Pleural opacification at day 30 (CXR)	
	59%	71% (difference: −12%, 95% CI −39–14%)	20%	9.5%	47%	54%
Patients resuming normal activity levels within 6 weeks post-admission	N/A		55%	43%	N/A	
Time from discharge to resuming normal activity levels, days	N/A		10 (4.5–18)	13 (6–18)	N/A	
Patients with treatment success, but persistent respiratory symptoms 6 weeks post-admission	N/A		45%	52%	N/A	
Serious adverse events	N/A		N/A		25.5%	21.4%
Hyperglycaemia	N/A		N/A		15.7%	7.1%
Relapse following clinical stability	N/A		N/A		35.3%	31.8%
Discharge without readmission following clinical stability	N/A		N/A		58.8%	68%
Readmission within 30 days of treatment	N/A		N/A		15.7%	10.7%
Other	No statistically significant differences in terms of clinical symptoms, vital signs, laboratory studies and effusion size on CXR at day 14 and 21		N/A		WBC at day 3 higher in dexamethasone group (estimated intergroup difference: 3.45×10^9 cells per L, 95% CI 1.75–5.14)* No differences in WBC at day 14 and 30 No differences in CRP or CXR at days 3, 14 and 30 No differences in the 36-item Short Form Health Survey questionnaire	

Data are presented as number (%), mean±SD or median (interquartile range) as presented in the original studies, unless stated otherwise. ODAPE: Optimal Duration of Antibiotics in Parapneumonic Effusions; SLIM: Short *versus* Long antibiotic course for pleural Infection Management; STOPPE: Steroid Therapy and Outcome of Parapneumonic Pleural Effusions; CXR: chest X-ray; WBC: white blood cells; CRP: C-reactive protein; N/A: not available. [#]: STOPPE trial did not have any predefined end-points, STOPPE data are presented in the respective cells to facilitate comparison. *: p<0.05, statistically significant result.

(three died from reasons unrelated to their pleuropulmonary infection, *i.e.* suicide, traumatic subdural haematoma, and septic shock 8 weeks after randomisation from bacteria other than the ones detected in pleural fluid; one was unavailable for thoracic imaging due to moving to another city), only 51 patients were evaluated for residual pleural thickening. Residual pleural thickening >10 mm was found in 59% and 71% (difference: −12%, 95% CI −39–14%) of patients in the short- and extended-regimen group, respectively. Given that the 95% confidence interval upper bound of this difference was above 10%, the non-inferiority criterion was not met.

SLIM trial

SLIM recruited 80 patients, 50 (63%) of whom were finally eligible for randomisation to the short- (n=25) or the long-course group (n=25). Approximately 70% of patients in both groups received metronidazole plus ampicillin–sulbactam (56–60%) or cephalosporin (12%) during hospitalisation. In the outpatient setting, however, combination treatment (*e.g.* metronidazole with amoxicillin–clavulanate or moxifloxacin) was less frequent (40% *versus* 52%) in the long-course group, the patients in this group more often received monotherapy with amoxicillin–clavulanate (24%) or moxifloxacin (24%). Outcome data were not available for two patients (one in each group), while the duration of antibiotics for four (16.7%) patients in the short-course group was longer (24–30 days) than the prespecified length. Thus, the primary outcome (*i.e.* treatment failure) was analysed both in the intention-to-treat (ITT) and the per protocol (PP) population. Treatment failure occurred in four (16.7%) and three (12.5%) patients from the short- and long-course group, respectively, and was diagnosed early after discharge (*i.e.* at the first follow-up visit at 2 weeks) in all but two patients from the long-course group (diagnosis at 6 weeks post-discharge). All patients with treatment failure from the long-course group and 50% of those from the short-course group were referred for surgery. The difference in the rate of treatment failure between the groups, was statistically insignificant both in the ITT (odds ratio: 0.714, 95% CI 0.142–3.600; p=0.683) and the PP population, even when adjusted for several covariates (odds ratio: 0.542, 95% CI 0.070–4.227; p=0.559). From the secondary outcomes, only the duration of antibiotic treatment differed significantly ($p<0.05$) between the groups (table 3). A lower incidence of residual pleural collection but more frequent antibiotic-related adverse events were seen in the long-course group while patients in the short-course group were less probable to have persistent symptoms and more probable to return earlier to daily activities.

STOPPE trial

In STOPPE, 374 patients were assessed for eligibility, 231 (62%) of whom were excluded due to fulfilling one or more of the exclusion criteria and 64 (17%) were lost due to other reasons (*e.g.* refusal to participate, discharge or transfer, referral for palliative care). Finally, 79 (21%) patients were randomised to standard clinical care plus dexamethasone (n=51) or placebo (n=28). Despite a trend towards earlier clinical stability in the placebo group, no significant difference was found between the groups (hazard ratio: 0.729, 95% CI 0.453–1.173; p=0.193) in this regard. Likewise, there was no difference in relapse rate following clinical stability (p=0.79), patients discharged without relapsing or being readmitted (p=0.48), rate of complete radiographic resolution of the effusion, CRP levels, patients that required pleural drainage procedures (p=0.60) or received intrapleural tissue plasminogen activator/DNase (p=0.259), duration of intravenous and total antibiotic therapy, incidence of adverse events, length of hospital stay, and physical (p=0.615) or mental (p=0.689) health components of the Short Form Health Survey questionnaire. Although the decline in peripheral leukocyte count was slower in patients receiving dexamethasone, presenting with higher counts at day 3 (difference: 3.45×10^9 cells per L, 95% CI 1.75–5.14; $p<0.001$), no difference was seen at days 14 and 30 between the groups. Patients receiving dexamethasone experienced twice as many hyperglycaemic events (15.7% *versus* 7.1%) and a higher readmission rate (15.7% *versus* 10.7%) compared with the placebo group, while two cases of delirium and three of serious worsening primary infection were also seen in this group.

Commentary

ODAPE and SLIM were the first RCTs evaluating the duration of antibiotics in pleural infection. They both found that shorter antibiotic courses are characterised by less adverse events while being equally efficacious to the longer courses for the treatment of pleural infection that is soon stabilised with medical treatment and does not require surgery. By contrast, STOPPE, the first RCT assessing the usefulness of corticosteroids in PPEs, showed no benefit from their use in unselected patients. However, these results should be interpreted cautiously due to the significant limitations of the studies.

Since their introduction in the 1940s, antibiotics have become one of the most frequently prescribed drug categories [12–14]. Indeed, the recognition of their efficacy in the treatment of infections was followed by an extensive wave of antibiotic prescription that was often unnecessary, such as in cases of inappropriate (*e.g.* for illnesses unresponsive to antibiotics) or excessive use (*e.g.* prolonged antibiotic courses) [13, 15].

This antibiotic overuse has been associated with the emergence of drug-resistant bacteria and serious side-effects, including antibiotic-related intestinal infections by *Clostridium difficile* [12, 13]. The fight against such consequences requires control of antibiotic use by prescription of antibiotics only when clearly indicated, selection of appropriate antibiotics for certain infections and avoidance of unnecessarily long durations of antibiotic treatment [16].

The duration of antibiotic courses has been traditionally guided by physician's habits and cultural norms rather than strong scientific data [17, 18]. The lack of such data was due to the limited trials examining the minimum effective antibiotic durations, because of the false belief that antibiotics are associated with only few serious adverse events [17, 18]. Moreover, physicians have been traditionally taught that antibiotic courses should be long enough to prevent the development of resistance by the treating bacteria, a theory that was essentially based on cases of resistance development from the use of suboptimal penicillin doses for the treatment of *Streptococcus pneumoniae* [19]. Both facts ultimately resulted in the frequent use of prolonged antibiotic courses in clinical practice [12, 13, 15–17]. During recent decades, however, mounting evidence supports shorter antibiotic courses, which seem to be non-inferior to the longer ones while causing fewer adverse events [20]. In a recent multicentre study, two-thirds of 6481 patients with pneumonia received longer antibiotic courses than the ones suggested by current guidelines and each excess day of antibiotic treatment was associated with a 5% increase in the odds for antibiotic-associated adverse events [21]. In pleural infection, robust data about the optimal duration of antibiotics are missing due to difficulties achieving adequately powered trials, mainly caused by the presence of multiple confounding factors (*e.g.* antibiotic penetration into the pleural cavity, patient immune status/response, infection origin, bacterial sensitivity to antibiotics) [3]. In the era of evidence-based medicine, however, the efficacy and safety of any therapeutic intervention should be evaluated in adequately powered RCTs.

ODAPE (n=55) and SLIM (n=50) were rendered significantly underpowered to detect differences between the study arms because of the limited number of included patients. The magnitude of this effect can be realised if one considers that only 19% (55 out of 284) of the patients required to achieve the desired statistical power of 80% were finally included in ODAPE trial. In other words, the final sample size (n=55) decreased the ability of ODAPE to detect differences between the groups (*i.e.* the study power) from the desired 80% to approximately 10% [22]. Due to the unmet sample size requirement, the ODAPE researchers used the 95% confidence interval of the difference in the rate of clinical success between the groups to determine whether this difference was significant or not, admitting that a difference of <10% would be non-significant. Considering that the 95% confidence interval expresses the range of values that likely include the true difference between the groups with a 95% degree of confidence, the observed 95% confidence interval (−3–9.7%) suggests that the true difference does not exceed 10% and is therefore nonsignificant. This approach seems to confirm the absence of differences between the groups, in a study that could not detect any due to limited power. Likewise, the omission of a power calculation in SLIM trial puts the integrity of the study conclusions in doubt. However, the high success rate (100% and 83%) of the short antibiotic courses in both trials supports the requirement for larger confirmatory studies.

Another limitation of ODAPE and SLIM was the exclusion of patients with severe disease. Both studies included only patients who responded or were deemed to respond adequately to medical treatment. Patients requiring surgery were excluded or underrepresented (no patient required surgery in ODAPE). Patients with hospital-acquired pleural infection, which is generally associated with worse prognosis, were excluded in ODAPE and underrepresented (16% of included patients) in the SLIM trial [8]. High-risk patients, such as those with a high RAPID score, were excluded in SLIM and underrepresented (20% of included patients) in the ODAPE trial. Finally, older patients, who are usually frailer, were absent from the SLIM trial (age range: 34–59 years). Thus, the findings of these trials can be applied to only a subgroup of patients, such as those with community-acquired pleural infection responding to medical treatment without the need for surgery. The fact that most patients in the ODAPE trial received intrapleural urokinase, which is not the standard of care in the treatment of pleural infection, further narrows the applicability of its findings [3].

In contrast to ODAPE and SLIM, STOPPE included patients with a wide range of characteristics, which rendered the study underpowered to detect any benefit from corticosteroids in specific patient subgroups. Most importantly, the indiscriminate enrolment of patients with pneumonia and pleural effusion may have led to the creation of a completely mixed population by including effusions of non-infectious cause. This might be supported by the fact that 22% of the sampled effusions were transudates, which is not typical for PPEs [1]. Moreover, the inclusion of PPEs irrespective of disease stage suggests that patients with both simple and complicated PPE may have been included. Considering that less than half (47%) of the included patients had their effusions sampled, the proportion of patients with pleural infection is unknown. The creation of a mixed population, along with the exploratory nature of the study regarding appropriate timing,

dose and duration of corticosteroids, may be responsible for the negative results. However, the absence of significant differences in the incidence of serious adverse events between the groups indicates the feasibility of corticosteroid use in such patients and allows further research in specific patient subgroups.

Conclusion

Short antibiotic courses may be non-inferior to the traditional longer courses for the treatment of community-acquired pleural infection that does not require surgery. Corticosteroids may offer no benefit in patients with community-acquired pneumonia and concomitant pleural effusion. Further studies are required to confirm these findings. Awaiting the results of such studies, it would be reasonable not to alter the traditional approaches in the treatment of pleural infection.

Conflict of interest: F. Chatzivasiloglou reports support for attending meetings and/or travel from Janssen-Cilag Pharmaceutical SACI (registration for ERS International Congress 2022); and is the Pleural Diseases Assembly Coordinator for the Hellenic Thoracic Society (unpaid position). The remaining authors have no conflicts of interest to disclose.

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