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The most appropriate therapeutic strategy for acute lower respiratory tract infections: a Delphi-based approach

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Lower respiratory tract infections (LRTIs) cause high morbidity and mortality worldwide. Empiric therapy often base the choice of antibiotic treatment on antibacterial spectrum of the agent rather than on its pharmacological properties or the pathogen resistance profile. Inappropriate prescribing leads to therapeutic failure and antibiotic resistance, with increasing direct and indirect health costs. A consensus on appropriate prescribing in LRTI therapy was appraised by this Delphi exercise, based on a panel of 70 pulmonologists, coordinated by a Scientific Committee of nine experts in respiratory medical care. Full or very high consensus was reached on several issues, including the role of oral cephalosporins in first-line treatments of LRTIs and the appropriateness of cefditoren, with balanced spectrum and high intrinsic activity, in LRTI treatment. Evidence-based medicine approach and a comprehensive process of disease management, from diagnosis to therapy and follow-up, should guide antibiotic prescribing.

Keywords: Delphi-based consensus, Antibiotic resistance, Prescribing appropriateness, LRTIs, Cephalosporins, Cefditoren

Introduction

Acute lower respiratory tract infections (LRTIs), like community-acquired pneumonia (CAP) and acute exacerbations of chronic bronchitis (AECB), are responsible for high morbidity and mortality worldwide. The burden of disease is greater than other infective, acute or chronic disorders (e.g. AIDS, diabetes or cancer) that are commonly considered pervasive health problems.[1] Bacterial infections account for the 80–90% of these respiratory infections and are the most frequent indications for antibiotic treatment: *S. pneumoniae* is the pathogen with highest incidence in CAP, while infections by *H. influenzae* and *M. catarrhalis* are more prevalent in AECB (Table 1).[2–4]

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Table 1 Percentage incidence of bacterial species within the spectrum of lower respiratory tract infection (LRTI)-associated pathogens

	CAP	AECB
S.pneumoniae	20–60	20–25
H. influenzae	3–10	40–45
M. catarrhalis	1–3	10–15
S. aureus, Pseudomonas	2–10	10–15
M. pneumoniae	5–50	10–15
C. pneumoniae	5–15	10–15

Notes: CAP: community-acquired pneumonia; AECB: acute exacerbations of chronic bronchitis.
Value are expressed as percentages.
Data from[2,4,21].

Antibiotic therapy aims not only at improving the clinical outcome, but also eradicating the targeted pathogens or reducing bacterial load.[5] Therefore, empiric therapy should select the right dose and the most appropriate duration of treatment to obtain the optimal clinical response, to minimize toxicity and to prevent the emergence of resistant pathogens.[6] However, the treatment strategy often emerges from the empirical approach of clinicians, who are prone to choose the best therapeutic agent among the antibiotics available on the market. Consequently, the rationale of the choice is based predominantly on the antibacterial spectrum of the molecule without considering the profiles of pathogen resistance to the same molecule or the pharmacological properties of the different antimicrobial drugs.[7] This may result in an inappropriate prescribing practice, which may explain both the therapeutic failure and the proliferating resistance to antibiotics by pathogens of the respiratory tract.

The lack of appropriateness in antibiotic prescribing practices may further aggravate the epidemiologic profile of the resistant pathogens, reducing the potential of antibiotic therapy. The consequence is the increase of health costs, which are not necessarily influenced using the most expensive antibiotic, but rather by the indirect costs. Pharmacoeconomics studies conducted in U.S. and Europe demonstrated that the therapeutic failure following the incorrect choice of the antibiotic (and/or of its dosage and administration schedule) may cause worsening of patient's conditions and hospitalization, which accounts for most of the total costs.[8–10]

This work aims at methodically and systematically defining a consensus on the most controversial and debated issues on the diagnostic and therapeutic approaches to LRTIs. The role of oral antibiotic therapy for the management of CAPs and AECBs will be examined, in particular. The final goal of our contribution is promoting the most appropriate use of antibiotics to maximize therapeutic outcome with minimal drug toxicity and to minimize the development of antibiotic resistance, in accordance with the recommendations from the most prestigious National and International health organizations.

Material and methods

To assess the consensus on appropriate prescribing of antibacterial agents for LRTI therapy, we used the Delphi methodology. This is a group-facilitative method based on the multistage process of a series of iterative rounds (or questionnaires), each followed by feedback responses or ranking, designed to verify in a given area of uncertainty within health sciences the convergence of opinion of an expert panel in search of the most reliable group consensus according to evidence-based medicine.[11] This method, which is becoming increasingly popular in health care research, overcomes the potential problem of group dynamics that may occur with decision-making committees.[12]

The Delphi process was developed over nearly eight months by the following steps: (i) establishment of a scientific steering committee of nine experts who were in charge preliminary of reviewing the literature and of developing the statements to be ranked; (ii) selection of an expert panel of specialists; (iii) first-round of online statement ranking by each panel expert; (iv) analysis of the results of round one, and second round of ranking of items that have not gained collective opinion; (v) final consensus meeting.

Scientific steering committee

Nine experts were identified among Italian institutions, as representative of different clinical specialties involved in medical care of patients with CAP, AECB and of exacerbations of chronic obstructive pulmonary disease (COPD) as well. Track record of publications, attendance to National and International meetings, participation to clinical trials, recognized expertise and/or academic rank were the selection criteria. The scientific steering committee defined 39 statements divided into the following four main topics:

(1) Issues in aetiology and antibiotic resistance involved in the process of prescribing antibiotics
(2) Pharmacologic issues involved in the practice of prescribing antibiotics
(3) Clinical considerations on the management of patients with CAP, AECB and COPD
(4) Pharmacoeconomics viewpoints on the practice of prescribing antibiotics

Panel of specialists

Seventy pulmonologists (MASTER working group) were selected from different Respiratory Units (Hospital or University based) or Respiratory Healthcare Structures as representative of the clinical practice in the field of respiratory disorder management in Italy.

Rounds

The statements developed by the steering committee were delivered to panel experts, who rated agreement or disagreement for each of the 39 statements, independently and blindly. Survey was performed online on a secured survey website (first round), using Verisign certificate SSL version 3 with 128-bit encryption. The responses of participants were collected and analyzed prior to the final consensus meeting (second round). Participants expressed their level

of agreement on each statement using a five-point Likert-type scale (1: disagree, 2: somewhat disagree, 3: neither agree nor disagree, 4: somewhat agree, 5: agree).

Data analysis

The results of Delphi exercise data analysis were expressed as percentage of respondents who scored an item either 4 (somewhat agree) or 5 (agree). For the purposes of the consensus statement, agreement among the respondents of ≥70% for each statement was considered consensus, according to previous Delphi studies.[13–15]

The scientific steering committee evaluated the responses and grouped those for which no consensus was reached and that were selected for the following step. After the individual and anonymous online survey, the participants (plus the nine members of the steering committee) attended a meeting to share the results of the first-round voting. After discussing the results, the 39 statements were voted again (once more blinded) using the same five-point scale.

Results

The panel of Italian experts performed the Delphi process and generated consensus opinions on 39 statements regarding different issues on the prescribing process of antibiotics for the management of patients with acute LRTIs. In details, the 39 statements were grouped per four areas within the following general concepts: (i) aetiology and antibiotic resistance; (ii) pharmacology; (iii) clinical practice; (iv) pharmacoeconomics (Table 2).

Table 2 Statements defined by the scientific steering committee into four main topics and submitted to the expert panel of the Delphi-based consensus. The percentage of consensus reached for each statement is reported

Statement	Consensus (%)
Topic 1: Issues in aetiology and antibiotic resistance involved in the process of prescribing antibiotics	
1.1 The aetiologic diagnosis in case of respiratory infections is still hard to be obtained. This also because microbiologic investigations are not frequently performed in the clinical practice of LRTIs. Therefore, treatment of these infections is necessarily empirical in most cases, driven by patient's risk factor evaluation and by local microbiology	96
1.2 The choice of the antibiotic for the empiric therapy of respiratory infections is based on the knowledge of the most likely bacterial aetiology and of the updated chemoresistance profile of the possibly involved pathogens	100
1.3 When choosing an antibiotic for empiric therapy, potential pathogens involved, local antibiotic resistance profile, patient's immunocompetence/immunodeficiency status, performance status of the patient and risk factors for specific pathogens must be evaluated	100
1.4 Antibiotics with resistance levels above the 10%-20% threshold should not be used in empiric therapy	71
1.5 Based on observed resistance profile, some antibiotics should not be regarded as first-choice agents for the empiric therapy of LRTIs. This refers to non-protected betalactams (amoxicillin), tetracyclins, trimethoprim/sulphametazole and macrolids in particular	72
1.6 *Streptococcus pneumoniae, Haemophilus spp.* and *Moraxella catarrhalis* are responsible for the 85–95% of cases of chronic bronchitis bacterial exacerbation. All these pathogens develop a significant increase of resistance	79
1.7 During COPD exacerbation, the antibacterial activities of aminopenicillins, macrolides, tetracyclins, oral cephalosporins on *Streptococcus pneumoniae, Haemophilus spp. and Moraxella catarrhalis* do not overlap	92
1.8 *Enterobacteriaceae* and *Pseudomonas aeruginosa* must be considered in aetiologic hypotheses in patients with severely compromised respiratory function (FEV_1 < 30%) and/or with radiological evidence of bronchectasis	95
1.9 All hospetalized patients with CAP must undergo to at least one set of hemoculture, irrespective of the severity of patient's conditions	41
1.10 Amongst 3rd-generation oral cephalosporins, cefditoren pivoxil has the highest intrinsic activity on Streptococcus pneumoniae, PEN-R strains included	100
1.11 The activities of fluoroquinonolones (ciprofloxacin, levofloxacin, moxyfloxacin) on *Streptococcus pneumonia* do not overlap	96
1.12 When an infection is suspected to be caused by resistant bacteria, the antibiotic with highest intrinsic activity must be used	90
1.13 When treating AECB, an highly active antibiotic against BLNAR (Betalactamase Negative Ampicillin Resistant) and BLPACR (Betalactamase-Positive Amoxicillin-Clavulanic Resistant) strains must be used to control the intra-species spread of *Haemophilus influentiae* resistance	78
Topic 2: Pharmacologic issues involved in the practice of prescribing antibiotics	
2.1 To identify the profile of exposure to the drug, for its ability not only to eradicate microorganisms, but also to impair the emergence of resistant subpopulation, the pharmacokinetics/pharmacodynamics relationship must be analyzed	98
2.2 The different pharmacokinetic/pharmacodynamic characteristics of oral cephalosporins (ceftibuten, cefixime, cefditoren pivoxil) establish both dosage and eradication efficacy of the antibiotic	100
2.3 Oral administration is the route of choice for home care of mild LRTIs, if neither contraindications/limitations to absorption nor other patient-related limiting conditions exist	98
2.4 Among third-generation oral cephalosporins, ceftibuten and cefixime display mainly a Gram-negative spectrum, while cefditoren has a balanced spectrum, including Gram+ e Gram- bacteria	96
2.5 In LRTI therapy with cephalosporin, initial dosage and the route of administration depend on the severity of patient's conditions	97
2.6 During LRTI oral therapy, the antibiotic dosage must not be reduced even in presence of clinical improvement and in absence of adverse events	96
2.7 In patients under poly-pharmacotherapy, oral betalactams are the safest antibiotics according to their pharmacological interaction profile	92
2.8 When switching from parenteral therapy with third-generation cephalosporins (cefotaxime, ceftriaxone) to oral therapy, the most appropriate option is cefditoren pivoxil, due to the similar spectrum and the better intrinsic activity	93

(*Continued*)

Table 2 (*Continued*).

Statement	Consensus (%)
Topic 3: Clinical considerations on the management of patients with CAP, AECB or COPD	
3.1 For treatment of pneumonia caused by *Chlamydophila pneumonia* and *Mycoplasma pneumonia,* macrolides can be used in monotherapy, mainly in adolescents and younger adults	87
3.2 Number and duration of antibiotic therapies performed by the patient in the past year can be a predictor of a bacterial infection resistant to previously used antibiotics	89
3.3 In respiratory infections, the evaluation of biomarker blood levels (e.g. reactive C protein or procalcitonin) is useful to determine indications, monitoring and discontinuation of antibiotic therapy	90
3.4 Patients with BPCO who undergo exacerbation with purulent sputum should receive antibiotic treatment	100
3.5 For community-acquired infections of the lower respiratory airways, betalactams should be regarded as first-choice antibiotics, also in monotherapy	77
3.6 In mild-moderate AECB and in elderly individuals with risk factors, oral cephalosporins must be considered as first-line treatment, while fluoroquinolone use must be restricted to more severe exacerbations, mainly in patients with bronchectasis	89
3.7 Sending to hospital and/or hospitalizing a CAP patient is a decision of clinical and welfare relevance, which should be supported by a given severity score (e.g. CRB-65, CURB-65 or Pneumonia severity index) and should evaluate the chances of a patient's accurate home care	100
3.8 The analysis of clinical efficacy of an empiric antibiotic treatment should not be performed before 48–72 h from the treatment start, on the basis of simple clinical and laboratory criteria	97
3.9 The switch from parenteral to oral antibiotic therapy must be driven by the clinical outcome of the patient and occurring when clinical stability is reached	96
3.10 In general, the antibiotic therapy for CAP should last minimum five days and not exceed eight days in responsive patients, irrespective of the causative pathogen	93
3.11 In general, the antibiotic therapy of COPD exacerbations should last minimum five days and not exceed eight days in responsive patients	90
3.12 Discharge of a hospitalized patient with LRTI can be evaluated when clinical stability is reached, in absence of other comorbidity exacerbations and of social issues	100
3.13 In a patient with CAP who responded to the antibiotic therapy, a control chest radiograph is not required before three weeks from therapy discontinuation	92
Topic 4: Pharmacoeconomics viewpoints on the prescribing practice of antibiotics	
4.1 The most appropriate choice of antibiotic therapy must consider the efficacy, as well as direct and indirect costs, including those related to the problem of antibiotic resistance	98
4.2 The social/environmental impact originated by the spread of antibiotic resistance is a priority of mine to take a therapeutic decision	94
4.3 In the treatment of LRTIs, the price of the initial antibiotic therapy does not represent the most affecting health care cost.	88
4.4 Method of administration and tolerability of the antibiotic are key issues to enhance adherence to treatment and therefore to limit the therapeutic failure	96
4.5 The switch from parenteral to oral antibiotic therapy reduces length and costs of hospitalization, and the risk of hospital-acquired infections, improving patient's quality of life as well	100

The overall response rate of Delphi first round was 100% (70 responding participants out of 70 total panellists) and that of second round was 76% (53 out of 70). After second-round voting a positive consensus was reached on 38 of 39 statements with agreement ranging from 71 to 100%. Total agreement (100%) was reached in 8 of 39 of the statements.

In Authors' view, the consensus opinions reached in 20 of the 39 statements appear of particular impact on appropriateness of prescribing practice and are selected for discussion, as outlined below.

Topic: issues in aetiology and antibiotic resistance involved in the process of prescribing antibiotics (Table 3)

The accurate aetiological diagnosis in LRTIs remains a difficult task still nowadays. The identification rate of the pathogen in hospitalized patients within controlled studies does not exceed 50% and these infections are often empirically treated.[7] The distribution of chemosensitive bacterial strains is geographically variable and updated information on a specific area is not frequently available. This leads to a risk of therapeutic failure ranging between 8 and 21% for AECB.[7,8] and also to underestimate the antibiotic resistance issue even if when patients are revisited for the same problem or present with AECB after a recent antibiotic treatment.

The microorganisms causing LRTIs have remained almost unchanged for the last years. *S.pneumoniae*, *H.influenzae* and *M.catarrhalis* are the main potential pathogens. More information has become available on the frequency of polymicrobial infections, including viral infections. Panton-Valentine leucocidin- producing *S.aureus* has emerged as a new cause of LRTIs, most often of severe CAP, although its occurrence remains currently uncommon.[16,17] Gram-negative nosocomial multidrug-resistant pathogens – such as *P.aeruginosa* – are more frequently isolated in patients with severe respiratory alterations or with a long history of hospitalization. Although no significant changes were identified in the aetiology of these syndromes, still frequency and clinical relevance of antimicrobial resistance remain important issues.

The expert panel reached consensus (71%) on avoiding the use in empiric therapy of antibiotics known to have a percentage of resistance above the 10–20% threshold, an opinion formulated by the study group of the Italian Group

for the Study of Antibiotic Resistance in Respiratory Infections (GIARIR).[7] In addition, based on the observed resistance profiles, several antibiotics such as non-protected betalactams (amoxicillin), tetracyclines, trimethoprim/sulphamethoxazole and macrolides, should never be used in empiric therapy (consensus = 72%).

In case of *S. pneumoniae* in particular, a constant increase of bacterial resistance was observed in the last seven years,[18,19] such as in Italy, where the percentage of strains not susceptible to penicillin (intermediate and resistant) has reached values close to 15% onwards increasing in a four-year period (6.9% in 2011; 12.1% in 2012; 14.6% in 2013; 14.8% in 2014; Figure 1) and, due to the acquisition of the erythromycin ribosomal methylation (*erm*B) gene, the incidence of resistance to macrolides is constantly growing with current values reaching 40–50%.[20] This high prevalence of erythromycin resistance prompted to the reassessment of the current use of this drug. High level of consensus (79%) has been reached on the major role of these species in increasing the levels of resistance.

On the contrary, no consensus was reached (41%) about the need of running at least one set of blood cultures in hospitalized patients with CAP, independently on how severe can be patient's conditions (Table 3). The unambiguous lack of consensus on this statement may be explained also by the existence of two inconsistent guidelines about the value of blood culture in the diagnosis of CAP. Guidelines of European Respiratory Society (ERS) and European Society for Clinical Microbiology and Infectious Diseases (ESCMID) recommend blood culture in all CAP patients who require hospitalization with a high level of evidence,[3] while those of the Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) recommend blood cultures for patients with severe CAP; blood cultures are also considered optional in all hospitalized patients with CAP but should be performed selectively.[21] The specialists involved in this Delphi consensus exercise may have been deployed in one or other of these two lines of thought.

The cephalosporin class of antimicrobial agents is known for its broad spectrum of activity, proven efficacy and favourable safety profile. However, even if all cephalosporins are equally active on Gram-negative bacteria (e.g. *Haemophilus*

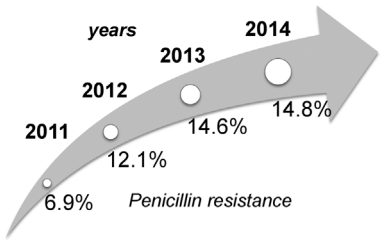

Figure 1 Constant increase of bacterial non-susceptibility to penicillin in *S. pneumoniae*, expressed as percentage of intermediate and resistant strains (% I+R) observed in Italy from 2011 to 2014 and further raising trend in the following years.

Table 3 Consensus on the management of acute LRTIs. Percentage of agreement to the statements of topic 1: Issues in aetiology and antibiotic resistance involved in the process of prescribing antibiotics

Statement	Panel responses				
	1	2	3	4	5
1.4 Antibiotics with resistance levels above the 10%-20% threshold should not be used in empiric therapy		29%			71%
1.5 Based on observed resistance profile, some antibiotics should not be regarded as first-choice agents for the empiric therapy of LRTIs. This refers to non-protected betalactams (amoxicillin), tetracyclines, trimethoprim/sulphametazole and macrolides in particular		28%			72%
1.6 *Streptococcus pneumoniae*, *Haemophilus spp.* and *Moraxella chatarrhalis* are responsible of the 85-95% of cases of chronic bronchitis bacterial exacerbation. all these pathogens develop a significant increase of resistance		21%			79%
1.9 All hospitalized patients with CAP must undergo to at least one set of hemoculture, irrespective of the severity of patient's conditions		59%			41%
1.10 Amongst 3rd-generation oral cephalosporins, cefditoren pivoxil has the highest intrinsic activity on *Streptococcus pneumoniae*, PEN-R strains included		0%			100%
1.13 When treating AECB, an highly active antibiotic against BLNAR (Betalactamase Negative Ampicillin Resistant) and BLPACR (Betalactamase Positive Amoxicillin-Clavulanic Resistant) strains must be used to control the intra-species spread of *Haemophilus influentiae* resistance		22%			78%

Legend: No consensus | Consensus

Note: Panel responses were: 1, Disagree; 2, Somewhat disagree; 3, Neither agree nor disagree; 4, Somewhat agree; 5, Agree.
Each percentage in the second column is the sum of subjects choosing 1-2-3, and the percentage in the third column is the sum of subjects selecting 4-5.

Table 4 Different spectrum of activity among oral cephalosporins on S. pneumoniae

Classification	Activity	Antibiotic	MIC_{90} (mg/L)			Ref.
			P_S	P_I	P_R	
1st generation	Prevalently active against Gram-positive bacteria	Cephalexin	na	128[(a)]	na	[55]
		Cefadroxil		>64[(a)]		
2nd generation	Less active than first generation against Gram-positive bacteria	Cefaclor	1	64	>64	[22,40]
		Cefprozil	0.25	8	>16	
	More active against Gram-negative bacteria, but poorly active against *H. influenzae and M. catarrhalis*	Cefuroxime	0.12	4	8	
3rd generation	Less active against Gram-positive bacteria, including *S. pneumoniae*	Cefpodoxime	0.06–0.12	2	4	[22,40]
		Cefixime	0.12–1	16	>16	
	Prevalently active against Gram-negative bacteria	Ceftibuten	0.25–4	8–16	>8–>16	
	Active against a broad spectrum of Gram-positive and Gram- negative bacteria	Cefditoren	0.015–0.03	0.25–0.50	0.5–1	[22,40]

Note: na, not available P_S penicillin-sensitive; P_I penicillin-intermediate; P_R penicillin-resistant.
[(a)]susceptibility to penicillin not determined.

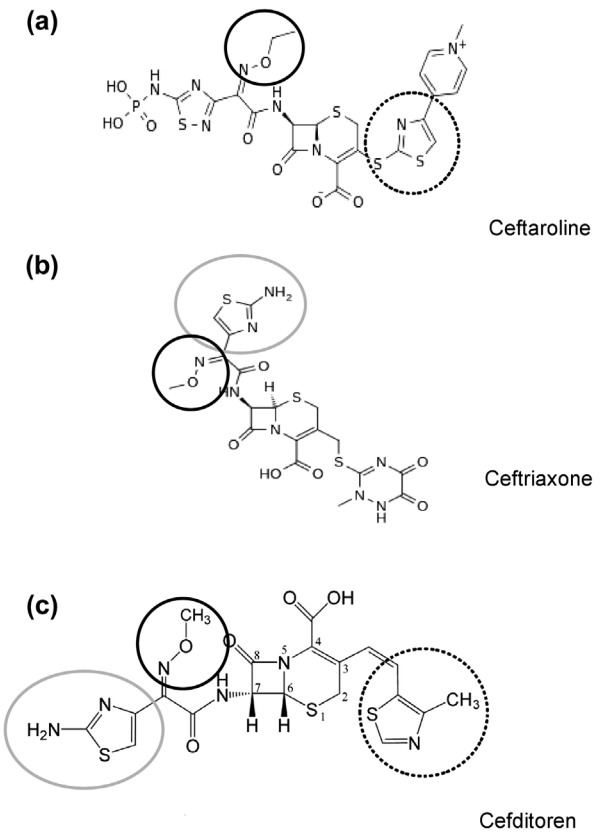

Figure 2 Structural formulas of three representative cephem molecules and functional groups determining spectrum activity. Ceftaroline (Fifth generation) (a) is characterized by the presence of the thiazole-pyridine rings in C3 position conferring broad-spectrum activity against Gram-positive species. Ceftriaxone (Third generation) (b) carries the methoxyimino group and the aminothiazole substitution in the C7 side chain, granting a good β-lactamase stability and a higher activity on Gram-negative bacteria. Cefditoren (Third generation) (c) possess all these functional groups and possess full spectrum of activity both on Gram-positive and Gram-negative bacteria. Black circle, methoxyimino group (beta-lactamase stability); grey circle, aminothiazole group (activity against Gram-); dashed circle, methylthiazole group (activity against Gram+).

spp, *Moraxella spp*), remarkable differences exist among the members of this class for Gram-positive species (e.g. *S. pneumoniae*) (Table 4). Several studies have been conducted to compare the pharmacokinetics/pharmacodynamics (PK/PD) parameters and the activity of the II- and III-generation oral cephalosporins available on the market.

In a study aimed at comparing *in vitro* activity of cefditoren with several other comparators against more than 2,000 isolates from community-acquired respiratory infections in Italy,[22] cefditoren resulted the most active antibiotic against all penicillin-susceptible strains of *S. pneumoniae* and *S. pyogenesis*, and slightly less potent on penicillin-resistant pneumococci. Moreover, cefditoren shared with levofloxacin the highest activity against methicillin susceptible staphylococcus aureus (MSSA), *K. pneumoniae* and *E. coli*. Together with levofloxacin and cefotaxime, cefditoren displayed the most potent antimicrobial activity against all strains of *H. influenza*, irrespective of their ampicillin resistance.[22] The structural basis of this strong antimicrobial activity lies on the high affinity of the cefditoren molecule for the Penicillin Binding Protein 2X (PBP 2X), responsible for cephalosporin resistance when mutated, as demonstrated by crystallographic analysis of the antibiotic-protein complex.[23] Consistently, the statement declaring cefditoren pivoxil the III-generation oral cephalosporin with the highest intrinsic activity on *S. pneumoniae*, penicillin-resistant strains included, attained full consensus (100%) in this Delphi consensus exercise.

Moreover, in addition of *S. pneumoniae* strains that are resistant to penicillin, macrolides or fluoroquinolones, new phenotypes of *H. influenzae* emerged alongside canonical β-lactamase- negative (BLN) and β-lactamase-positive (BLP) strains: β-lactamase-negative ampicillin-resistant (BLNAR) and β-lactamase-positive amoxicillin/clavulanic acid-resistant (BLPACR). The carriage of these strains, characterized by mutations of the *ftsI* gene encoding the

PBP 3 protein, caused recent concern for its increasing occurrence in several European countries.[24–26] When treating AECB, to prevent the intra-species diffusion of BLNAR and BLPACR resistant strains it is mandatory using antibiotics able to target also the emergent strains. The expert panel reached consensus (78%) also on this statement (Table 3). According to a pharmacodynamics study, cefditoren displayed higher antibacterial activity than cefuroxime and amoxicillin/clavulanic acid against a mixed population of *H. influenzae* strains, including BLNAR and BLPACR phenotypes.[27]

Topic: pharmacologic issues involved in the practice of prescribing antibiotics (Table 5)

The management of antimicrobial therapy benefits from knowing the PK/PD parameters of the antibiotic in use, which are useful predictors of the therapeutic efficacy. To obtain a bacterial eradication and not only a clinical result, dose and time of administration of an antibiotic must be adequate to its PK/PD profile. For time-dependent antibiotics like β-lactams, the parameter that better defines bactericidal efficacy and that allows controlling the emergence of resistant strains is T > MIC.[28] This is the time the serum concentration of the agent maintains above the minimum inhibitory concentration (MIC) for a given pathogen, expressed as percentage of dose interval.[29] On the contrary, in case of concentration-dependent antibiotics, such as fluoroquinolones and semi-synthetic macrolides (azithromycin and clarithromycin), the pharmacological goal is obtained by attaining adequate values of the ratio between either the area under the plasma concentration versus time curve (AUC) and the MIC (AUC/MIC), or the peak plasma concentration (Cmax) and the MIC (Cmax/MIC).[30] Even in empiric therapy, when these parameters reach optimal values, both the clinical/microbiological efficacy is ensured and the emergence of resistant bacteria is hampered.[31] As a matter of fact, an almost maximal consensus (98%) has been reached on the importance of the PK/PD profile of the antibiotic of choice for the patient's treatment and to avoid an increase of microbial resistance.

An antibiotic for the effective therapy of LRTIs should be; (i) active on the most common isolates and on strains resistant to other agents; (ii) provide the highest *in vitro* activity; (iii) display pharmacodynamics features to make pathogen eradication very likely to occur. The structure-activity relationship of the different cephalosporins fully explains their versatility in terms of antimicrobial activity against both Gram-positive and Gram-negative species. Starting from second-generation cephalosporins, the presence of a 2-metoxyimino group (protecting from β-lactamases) and of an aminothiazole substitution in the C7 side chain, as well as a thiazole-derivative group as the C3 side chain of the cephem molecular skeleton have been shown to enhance antibacterial activity.[23] These substitutions also play as discriminators between Gram-positive and Gram-negative targets (Figure 2). The C3 substitution is particularly important for activity against Gram-positive pathogens. The later generation ceftaroline, for example, has a broad-spectrum activity against Gram-positive species (including methicillin-resistant *Staphylococcus* strains), because of the presence of thiazole-pyridine rings in C3 position, but it displays a reduced activity on Gram-negative species, because of the lack of the aminothiazole substitution in the C7 side chain (Figure 2a). On the other hand, ceftriaxone, a third-generation molecule (Figure 2b), having the metoxyimino group and the aminothiazole substitution in the C7 side chain, has a good β-lactamase stability and a higher activity on Gram-negative bacteria,

Table 5 Consensus on the management of acute LRTIs. Percentage of agreement to the statements of topic 2: Pharmacological issues involved in the practice of prescribing antibiotics

	Panel responses				
Statement	**1**	**2**	**3**	**4**	**5**
2.1 To identify the profile of exposure to the drug, for its ability not only to eradicate microorganisms, but also to impair the emergence of resistant subpopulation, the pharmacokinetics/pharmacodynamics relationship must be analyzed		2%		98%	
2.3 Oral administration is the route of choice for home care of mild LRTIs, if neither contraindications/limitations to absorption nor other patient-related limiting conditions exist		2%		98%	
2.4 Among third-generation oral cephalosporins, ceftibuten and cefixime display mainly a Gram-negative spectrum, while cefditoren has a balanced spectrum including Gram+ e Gram- bacteria		4%		96%	
2.5 In LRTI therapy with cephalosporin, initial dosage and the route of administration depend on the severity of patient's conditions		3%		97%	
2.6 During LRTI oral therapy the antibiotic dosage must not be reduced even in presence of clinical improvement and in absence of adverse events		4%		96%	
2.7 In patients under poly-pharmacotherapy oral betalactams are the safest antibiotics according to their pharmacological interaction profile		8%		92%	
2.8 When switching from parenteral therapy with third-generation cephalosporins (cefotaxime, ceftriaxone) to oral therapy, the most appropriate option is cefditoren pivoxil, due to the similar spectrum and the better intrinsic activity		7%		93%	

Legend: No consensus | Consensus

Note: Panel responses were: 1, Disagree; 2, Somewhat disagree; 3, Neither agree nor disagree; 4, Somewhat agree; 5, Agree.
Each percentage in the second column is the sum of subjects choosing 1-2-3, and the percentage in the third column is the sum of subjects selecting 4-5.

but lacking the thiazole substitution in C3, has a lower potency against Gram-positive species.[32] Among oral cephalosporins, cefditoren essentially fulfils these conditions (Figure 2c) and holds a balanced antimicrobial spectrum that includes the three major pathogens of community-acquired LRTIs: *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*.[5] Very high consensus has been reached (96%) on the statement that amongst III-generation oral cephalosporins, the spectrum of ceftibuten and cefixime is mainly directed against Gram-negative bacteria, while the one of cefditoren is more balanced, including both Gram-positive and Gram-negative species (Table 5).

Oral administration is considered as the route of choice for the home care of mild LRTIs. Almost maximal consensus (98%) has been reached on this statement by the panel (Table 5). All oral cephalosporins have a relatively short half-life, therefore – considering their time-dependent efficacy – daily dosage should provide for at least two administrations. This ensures that concentrations above the MIC should be adequately maintained for a sufficiently long time interval along the 24-h period.[28]

The information on PK/PD features of the different classes of antibiotics offer a useful tool to the clinician for the choice of the most appropriate drug and of the most effective dose and route of administration in the therapy of LRTIs. The panel reached an almost complete agreement (97%) on the essential role of patient's disease severity in determining the initial dose and the route of administration of cephalosporins for the treatment of LRTIs. Several studies, including the multicenter ARISE project, demonstrated that the PK/PD aspects of cefditoren, mainly at a dosage of 400 mg/12 h, can produce adequate and effective concentrations for a time-dependent antibiotic, making this cephem derivative an antimicrobial agent of choice against both AECB and CAP.[7,33,34]

As far as adverse events and safety of antibiotics are concerned, macrolides have a quite high incidence of adverse events at gastrointestinal level, also due to the stimulatory effect on peristalsis and variable degrees of hepatotoxicity within the class.[35] Moreover, both macrolides and fluoroquinolones are inhibitors of cytochrome P450 enzymes, causing interactions with many different drugs, including HMG-CoA reductase inhibitors, calcium channel blockers, warfarin, benzodiazepines and other different drugs frequently used by elderly patients. In the case of fluoroquinolone class, a structure–adverse event relationship exists according to the different molecular features of these antimicrobial agents.[36] Inhibition of GABA system and stimulation of glutamate pathways account for the effects of fluoroquinolones on central nervous system. A QT interval prolongation has been observed at cardiac level.[37] Moreover, tendinopathy and Achilles tendon rupture have been associated with the use of several fluoroquinolone drugs.[38]

Cephalosporins have fewer adverse events than other antimicrobial agents currently used, with very rare risks of anaphylactic shock. The incidence of allergic reactions is approximately 1/10 of those associated with penicillin treatment and very few interactions have been observed with other drugs, mostly because the hepatic P450 cytochrome system is not affected by these β-lactam derivatives.[39]

Oral cephalosporins are generally well tolerated and treatment discontinuation with cefditoren, as a consequence of adverse events, has been observed only in 2.6% of patients.[40] The safety profile of cefditoren regarding the pharmacological interactions can be favourable in the clinical practice, especially in patients with comorbidities.[5] High consensus was reached (92%) on oral beta-lactams considered as the safest antibiotics with respect to the pharmacological interaction profile in patients under poly-pharmacotherapy (Table 5).

Hospitalized patients with CAP are usually treated with intravenous administration of antibiotics to maximize the drug concentration in the tissues. However, early switch from parenteral to oral antibiotic administration (switch-therapy or sequential therapy) has been demonstrated safe and suitable to reduce hospital stay.[41] According to the guidelines of US IDSA/ATS and of the European Respiratory Society/European Society of Clinical Microbiology and Infectious Diseases (ERS/ESCMID), the switch from parenteral to oral therapy is safe when patients reach hemodynamic and clinical stability.[3,21] Approximately 70% of hospitalized CAP patients are candidates for sequential therapy after 72 h, provided that clinical stability is reached.[42] The characteristics of oral antibiotics to be considered for the switch therapy are: (i) similar antimicrobial spectrum; (ii) high bioavailability; (iii) administration time 12–24 h; (iv) good tolerability.[43] The expert panel reached a high level of consensus (93%) on cefditoren pivoxil as the most adequate option for the switch therapy from parenteral third-generation cephalosporins (like cefotaxime or ceftriaxone) to oral therapy, because of the similar spectrum and the highest intrinsic activity. A recommendation should be issued to clinicians to perform, when possible, a sequential antibiotic therapy (i.e. the switch from parenteral to oral therapy) with no dosage reduction, unless in the presence of adverse events. A very high consensus (96%) was reached by the panel on this statement (Table 5). Furthermore, oral route is the ideal administration route in 'compliant' patients with mild LRTIs.

Topic: clinical considerations on the management of patients with CAP, AECB or COPD EXACERBATIONS (Table 6)

The choice of the most appropriate antibacterial agent, the identification and stratification of patients and the optimal duration of the therapy are main issues in the clinical management of LRTIs, while differences exist among recommendations of the different guidelines. On the basis of the antibiotic resistance emerged in recent years, some

Table 6 Consensus on the management of acute LRTIs. Percentage of agreement to the statements of topic 3: Clinical considerations on the management of patients with CAP, AECB and COPD

	Panel responses				
Statement	**1**	**2**	**3**	**4**	**5**
3.2 Number and duration of antibiotic therapies performed by the patient in the past year can be a predictor of a bacterial infection resistant to previously used antibiotics		11%		89%	
3.5 For community-acquired infections of the lower respiratory airways, beta-lactams should be regarded as first-choice antibiotics, also in monotherapy		23%		77%	
3.6 In mild-moderate AECB and in elderly individuals with risk factors, oral cephalosporins must be considered as first-line treatment, while fluoroquinolone use must be restricted to more severe flare up, in patients with bronchiectasis in particular		11%		89%	
3.10 In general, the antibiotic therapy for CAP should last minimum 5 days and not exceed 8 days in responsive patients, irrespective of the causative pathogen		7%		93%	
3.11 In general, the antibiotic therapy of COPD exacerbations should last minimum 5 days and not exceed 8 days in responsive patients		10		90%	

Legend: No consensus | Consensus

Note: Panel responses were: 1, Disagree; 2, Somewhat disagree; 3, Neither agree nor disagree; 4, Somewhat agree; 5, Agree.
Each percentage in the second column is the sum of subjects choosing 1-2-3, and the percentage in the third column is the sum of subjects selecting 4-5.

antimicrobial agents should not be considered for empirical therapy.[7] (Table 6).

The guidelines of the ERS/ESCMID for the management of antibiotic therapy of LRTIs indicate amoxicillin and tetracycline as 'preferred' antibiotics when aiming at minimal damage and based on a wide experience in clinical practice. Moreover, among cephalosporins, cefpodoxime and cefditoren prove to be more active than cefuroxime and cefprozil against *S. pneumoniae*.[3] The guidelines of the Canadian Thoracic Society distinguish the antibiotic choice according to disease severity and presence of common risk factors of COPD in the patient.[44]

A comprehensive review of the European national guidelines for the COPD management in the last seven years revealed a remarkable diversity in clinical and functional classification of COPD. Among different countries, there is a general concordance for the choice of treatments, diagnostic criteria and use of long-lasting bronchodilators, while the definition of patient phenotype subgroups and stratification are considerably different.[45]

It is of relevance the existence of evaluation criteria on the most appropriate antibiotic therapy based on the severity of COPD exacerbation. The guidelines of the Canadian Thoracic Society recommend the use of antibiotics in the presence of purulent sputum, while in case of mild bronchopathy the indication is to not administer antibiotics.[44] Further stratification criteria are based on the comorbidity and the pathogens involved. Groups are identified based on: (i) non-complicated COPD (group A) for which no antibiotic treatment is required; (ii) mild-moderate COPD with no risk factors for *P. aeruginosa* (group B) and with risk factors for this pathogen (group C). Indications for different antibiotics are given for the groups B and C.[3] In cases of COPD-bronchiectasis overlap syndrome, for the appropriate treatment of exacerbated non-cystic fibrosis-related bronchiectasis, the empirical antibiotic therapy should be adjusted or modified according to the results of sputum culture.[3] European guidelines and evidence from randomized controlled trials have been recently reviewed, revealing that inhaled antibiotic therapy emerges among the current approaches for non-cystic fibrosis bronchiectasis to maximize local drug concentrations and to reduce resistance risks.[46]

The most appropriate duration of treatment was defined by the ERS/ESCMID guidelines as not exceeding eight days in CAP responsive patients. Moreover, evaluation of biomarkers as procalcitonin are recommended to verify the efficacy of the treatment and to modulate its duration.[3] The guidelines of the British Thoracic Society recommend seven days of appropriate antibiotics for CAP patients with mild-moderate severity, while a longer therapy, up to 14 or 21 days, can be adopted in the presence of relevant bacterial species (e.g. *S. aureus*), underscoring the importance of having complete microbiological information for the best management of LRTIs.[47] The US ATS/IDSA consensus guidelines recommend that patients with CAP should be treated for a minimum of five days, according to their clinical conditions and indicate a longer duration of therapy only after bacteremia is present and pathogens are identified.[21] In case of exacerbation of COPD, the most recent guidelines of Global Initiative for Chronic Obstructive Lung Disease (GOLD) and of the Italian Federation of Hospital Internal Medicine (FADOI) recommend a duration of antibiotic treatment of 5–10 days.[48,49] The updated guidelines of the National Institute for Health and Care Excellence (NICE) give no recommendation on treatment duration, and the criteria for antibiotics use to treat exacerbations of COPD include a history of more purulent sputum.[50] In an ATS/ERS position paper no criteria of duration are defined, antibiotics use is indicated as first-line treatment for ambulatory patients.[51]

The panel of experts agreed (77% agreement) that betalactams should be contemplated among the first-choice antibiotics for the treatment of community-acquired LRTIs. Consensus was reached on the concept that the number and the duration of past year antibiotic treatments are predictive of a bacterial infection resistant to previously used antibiotics (89% agreement). Regarding the duration of antibiotic treatment, consensus was reached on a maximal eight days and a minimal five-day duration for responsive patients with CAP, irrespective of the pathogen involved (93% agreement), and for patients with exacerbated COPD (90% agreement). An evident consensus (89%) was reached on oral cephalosporins as first-line treatment of mild-moderate AECB in elderly patients with risk factors, while the use of fluoroquinolones should be limited to more severe exacerbations, especially in patients with bronchiectasis.

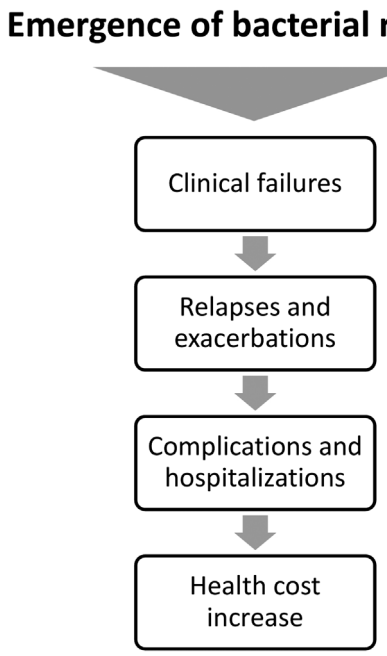

Figure 3 Schematic representation portraying the consequences of the emergence of bacterial resistance to antibiotics. The risk of therapeutic failure favours relapses and exacerbation of LRTI symptoms, leading to increased incidence of hospitalization with consequent increase of health costs. This scenario abates the cost effectiveness of antibacterial therapy.

Topic: pharmacoeconomics viewpoints on the prescribing practice of antibiotics (Table 7)

The emergence of bacterial resistance to antibiotics enhances the risk of therapeutic failure, increasing the health costs related to higher hospitalization rates and reducing the cost effectiveness of antibacterial therapy (Figure 3).[52] However, costs associated with antibacterial resistance are rarely included in pricing decisions as they should be when choosing the most appropriate antibiotic for the treatment of LRTIs.[10] Inadequate antibiotic treatment may frequently lead to hospitalization due to worsening of patient's conditions or to therapeutic failure, whose incidence was found up to 21% in case of AECBs[8] and that is accompanied to a many-fold increase of health costs. The analysis of the joint working group of the European Centre for Disease Prevention and Control/European Medicines (ECDC/EMA) revealed that in the European Union alone drug-resistant bacteria are estimated to cause 25,000 deaths and cost more than $ 1.5 billion every year in healthcare expenses and productivity losses.[53] Therefore, the choice of the most appropriate antibiotic is crucial also from the pharmacoeconomics point of view, aimed at obtaining a therapeutic success from the initial treatment. It has been estimated that for LRTIs, the influence on the total health care cost of the initial antibiotic treatment is 18% in absence of hospitalization and 10% in case of hospitalization[9] and pharmacoeconomics evidence indicates that the first-line use of more expensive antibiotics may minimize treatment failure and associated high economic burden, leading to global cost effectiveness[8–10] Another important option for health cost avoidance is the switch-therapy, from parenteral to oral route of antibiotic administration.[54]

In view of the possible containment of health costs in LRTIs, this Delphi exercise reached a high level of consensus (88%) on the non-decisive role played by the price of the antibiotic used in first-line treatment of LRTIs. For the most appropriate choice of antimicrobial therapy almost global consensus (98%) was reached on the necessity of taking in consideration the therapeutic efficacy, as well as direct and indirect costs, including those related to the consequence of antibiotic resistance (Table 7).

Table 7 Consensus on the management of acute LRTIs. Percentage of agreement to the statements of topic 4: Pharmacoeconomics viewpoints on the prescribing practice of antibiotics

	Panel responses				
Statement	**1**	**2**	**3**	**4**	**5**
4.1 The most appropriate choice of antibiotic therapy must consider the efficacy, as well as direct and indirect costs, including those related to the problem of antibiotic resistance		2%		98%	
4.3 In the treatment of LRTIs the price of the initial antibiotic therapy does not represent the most affecting health care cost.		12%		88%	

Legend: No consensus | Consensus

Note: Panel responses were: 1, Disagree; 2, Somewhat disagree; 3, Neither agree nor disagree; 4, Somewhat agree; 5, Agree.
Each percentage in the second column is the sum of subjects choosing 1-2-3, and the percentage in the third column is the sum of subjects selecting 4-5.

Discussion

Most of LRTIs, like CAP and AECB, which account for high morbidity and mortality worldwide, are of bacterial origin and represent the indication for the treatment with antibiotics. However, the inappropriate choice of the antibiotics and their use may further aggravate the increasing incidence of resistant pathogens, with the consequent reduction of the antibiotic therapeutic potential.[7]

The Delphi consensus exercise performed by this study reached consensus on many statements regarding debated issues on the appropriateness of prescribing antibiotics for the treatment of LRTIs. The following statement reached the highest level of consensus:

- In empiric therapy, antibiotics characterized by a resistance profile above the 10%-20% threshold and the non-protected betalactams should be avoided.
- For LRTI therapy, oral cephalosporins are often preferred among betalactams for their spectrum of action, resistance to betalactamase and good tolerability profile. Particularly, patients with LRTIs in poly-pharmacochemotherapy benefit from antibiotics with minimal drug interactions.[5]
- Amongst III-generation oral cephalosporins, the spectrum of cefditoren is particularly balanced, including both Gram-positive and Gram-negative species. The experts expressed the opinion that, due to its high intrinsic activity, cefditoren appears as an appropriate agent for either the treatment of LRTIs and for parenteral to oral switch therapy as well. Moreover, cefditoren at 400 mg dosage every 12 h ensures the coverage of penicillin-resistant Pneumococcal strains.[7,33,34]
- Oral cephalosporins can be included among the first-line treatments of mild-moderate AECB in elderly patients with risk factors, while the use of fluoroquinolones should be limited to more severe exacerbations, especially in patients with bronchiectasis.
- The price of the antibiotic used in first-line treatment has a minimum impact on the overall costs of LRTI management, while indirect costs related to the failures caused by bacterial resistance may have a considerable influence.
- The appropriateness of prescribing antibiotics should consider not only therapeutic efficacy and pharmacoeconomics considerations, but also a comprehensive process of disease management, from the diagnostic-therapeutic steps to the patient's follow-up.

This study has some strengths and limitations as well. *Strenghts:* the study employed Delphi method for the first time in the field of antibiotics therapy to verify the consensus on a series of statements concerning issues about diagnostic and therapeutic approaches to LRTIs. This technique is a robust instrument used also for the development of guidelines based on the clinical experience and the viewpoints of the specialist experts involved. The methodology ensures the free expression of ideas in an anonymous fashion to avoid the influence of group dynamics. *Limitations:* the number of participants to the first and the second rounds were different. Moreover, this Delphi consensus exercise portraits a picture that is limited to the Italian clinical practice. Further similar studies and/or studies involving a broader panellist board will hopefully foster the discussion on these important issues with the medical community.

In conclusion, the empiric approach for the choice of the most appropriate antibiotic in LRTIs should be reconsidered in view of evidence-based medicine, as indicated by the results of this Delphi study.

Declaration of interest

FB has received research grants from Chiesi, Pfizer and Zambon, congress lecture fees from Astrazeneca, Boehringer Ingelheim, Chiesi, Dompe, Guidotti-Malesci, Grifols, InnovaPharma, Menarini, Novartis, GSK, Pfizer, Teva and Zambon, and consultancy fees from AstraZeneca, Menarini, Mundipharma, Novartis, GSK, Teva and Pfizer. SS has received research grants from Astra Zeneca, Basilea Pharma, Pfizer, Zambon, DMG; Consultancy and lecture fee from MSD. MG has received research grants from Thermo Fisher Diagnostics SPA. Advisor/Consultant and lecture fee from Angelini, Astellas, Basilea, MSD, Sanofi, Zambon, Guidotti, Malesci. All the other Authors report no declaration of interest.

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