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REVIEW

Burden of Community-Acquired Pneumonia and Unmet Clinical Needs

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ABSTRACT

Community-acquired pneumonia (CAP) is the leading cause of death among infectious diseases and an important health problem, having considerable implications for healthcare systems worldwide. Despite important advances in prevention through vaccines, new rapid diagnostic tests and antibiotics, CAP management still has significant drawbacks. Mortality remains very high in severely ill patients presenting with respiratory failure or shock but is also high in the elderly. Even after a CAP episode, higher risk of death remains during a long period, a risk mainly driven by inflammation and patient-related co-morbidities. CAP microbiology has been altered by new molecular diagnostic tests that have turned viruses into the most identified pathogens, notwithstanding uncertainties about the specific role of each virus in CAP pathogenesis. Pneumococcal vaccines also impacted CAP etiology and thus had changed *Streptococcus pneumoniae* circulating serotypes. Pathogens from specific regions should also be kept in mind when treating CAP. New antibiotics for CAP treatment were not tested in severely ill patients and focused on multidrug-resistant pathogens that are unrelated to CAP, limiting their general use and indications for intensive care unit (ICU) patients. Similarly, CAP management could be personalized through the use of adjunctive therapies that showed outcome improvements in particular patient groups. Although pneumococcal vaccination was only convincingly shown to reduce invasive pneumococcal disease, with a less significant effect in pneumococcal CAP, it remains the best therapeutic intervention to prevent bacterial CAP. Further research in CAP is needed to reduce its population impact and improve individual outcomes.

Keywords: CAP; Community-acquired pneumonia; Epidemiology; Infectious disease

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Key Summary Points

Community-acquired pneumonia (CAP) is a major health concern, because it is a very frequent and deadly condition.

CAP etiology is changing owing to the recognized importance of viruses, pneumococcal and influenza vaccines.

New drugs were developed to treat CAP; however, most of them focus on non-severe CAP.

Despite the frequency of CAP, several recommendations are based on low quality evidence. We have therefore defined several unmet clinical needs to promote research on CAP.

INTRODUCTION

Community-acquired pneumonia (CAP) is a frequent and deadly infection, having considerable implications for healthcare systems worldwide. CAP is responsible globally for 3 million deaths annually [1]. Poor outcomes are usually related to CAP severity and patient characteristics and co-morbidities.

Some recent advances emphasise in the importance of continuous research in CAP. CAP classification has varied over the last 20 years. Recently, American guidelines [2] abandoned healthcare-associated pneumonia (HCAP) because of the lack of evidence showing differences in microbiology of CAP and HCAP. This definition change could introduce differences in epidemiological reporting. Important advances in CAP have also been reported since pneumococcal vaccines and diagnostic tests for viruses. Recently, *Nature Medicine* published the first use of phages to treat a multidrug-resistant (MDR) microorganism [3] and *Lancet Infectious Diseases* reported the first use of pneumolysin in severe CAP treatment added to standard of care in a phase II trial [4]. These advances emphasise the importance of continuously updating CAP management and research and development.

In this review, we aim to provide a perspective of CAP burden that is critical to allocating resources to improve patient outcomes and also to support new research focused on unmet clinical needs. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

BURDEN OF COMMUNITY-ACQUIRED PNEUMONIA

CAP Incidence

In Europe, CAP incidence varies widely ranging from 20.6/10,000 in Iceland [5] to 79.9/10,000 person-years in the UK [6]. Data from Italy [7] in adults (over 15 years of age) between 2005 and 2019 reported CAP incidence between 29.3 and 30.6 per 10,000 inhabitants and a hospitalization rate lower than 10% within 60 days from diagnosis. In France, CAP incidence is estimated as 47 per 10,000 person-years [8] with 7% of patients being admitted in the 30-day period after CAP diagnosis.

In the USA, in adults under 65 years old, CAP incidence varies between 24.8/10,000 person-years [9] and 106/10,000 person-years [10]. Moreover, as expected, elderly people have a higher incidence, representing 63.0/10,000 person-years in 65–79-year-olds and reaching 164.3/10,000 person-years after 80 years old. A study in Latin America (including Argentina, Paraguay and Uruguay) reported incidence varying between 4.8 and 110/10,000 person-years in people aged 18–-64 years and 109–294/10,000 person-years in those over 65 years [11]. Another study in Latin America (Argentina, Brazil, Chile, Colombia, Mexico and Venezuela) reported CAP incidence varying between 32.6 and 80.4/10,000 person-years in a population over 50 years [12].

South Korea has an incidence rate of 62.6/10,000 person-years [13] with high importance of pneumococcal pneumonia [14]. CAP incidence in Japan in middle-aged adults (55–-64 years) is 65/10,000 person-years, increasing

markedly over age to 169 and 434/10,000 person-years in adults aged 65–74 years and 75–-84 years, respectively. A recent study of three Asian countries [15] reported that CAP is responsible for 1424.5, 420.5 and 98.8 episodes per 10,000 discharges in the Philippines, Indonesia and Malaysia, respectively. In China, CAP incidence is estimated as 29.8–221.0 per 10,000 admissions including children [16]. In Australia, a study between 2011 and 2013 reported an incidence of 24.5/10,000 person-years [17] in patients older than 20 years. An Australian study estimated CAP incidence in all age groups (including children) as 161.3/10,000, rising to 319.3/10,000 and 659.9/10,000 person-years in patients between 65 and 74 years and over 75 years, respectively [18]. A retrospective analysis in New Zealand estimates CAP incidence as 85/10,000 in the general population and 188.2/10,000 in patients older than 65 years [19]. Table 1 summarizes global data on CAP incidence in adults.

To properly analyze this data it is important to keep in mind that the real clinical incidence of CAP is difficult to determine because of differences in reporting and case selection from epidemiological studies. CAP notification is optional even in developed countries, except when presenting as invasive pneumococcal disease (when CAP is accompanied by the identification of pneumococcus in sterile fluids such as blood, cerebrospinal fluid, and pleural, joint or peritoneal fluid) and Legionnaires disease in some countries. Worldwide differences in access to healthcare services also preclude direct comparison of incidence [20]. Furthermore, scarce data are available from primary care or representing patients treated in ambulatory settings. Moreover, CAP incidence varies considerably according to geographic location, study methods, case definition and study population [21, 22]. CAP incidence varies and is also highly influenced by age and co-morbidities (such as chronic obstructive pulmonary disease, diabetes mellitus, renal failure, congestive heart failure, coronary artery disease and liver disease). A seasonal effect that doubles the rate of pneumonia in the winter months impacts, additionally, incidence studies [23].

CAP Mortality

According to the World Health Organisation (WHO) data, lower respiratory tract infections are the primary infective cause of death globally accounting for 6.1% of deaths [24]. The Global Burden of Disease 2016 Study showed that deaths from low respiratory tract infections decreased both in the total number of deaths 8.2% (95% UI, − 12.4, − 3.9) and age-standardized rates 22.4% (95% UI, − 25.3, − 18.9), from 2006 to 2016 [25]. In the USA, CAP causes around 102,000 deaths per year, a mortality of 13%, 23.4% and 30.6% at 1 month, 6 months and 12 months, respectively [26]. CAP alone is responsible for at least 23,000 deaths annually in Europe [27]. One-year CAP mortality in Canada is estimated as 28% [28]. In the Asia–Pacific region CAP mortality is estimated between 1.1% and 30% [29]. In low-income countries, mortality tends to be higher, as proved in a study addressing mortality in low-income countries that showed higher mortality than in high-income countries, reporting a mortality rate of 23% in Cambodia, 19% in Senegal, 18% in Uganda and 16% in the Central African Republic [30].

Mortality occurs largely in hospitalized patients (6–20%) [22, 26, 31], but it varies widely according to treatment setting and severity disease, while mortality in primary care and ambulatory patients is inferior to 1% in most of the population, rising in patients over 65 years [7, 8]. One-ninth of patients hospitalized with CAP will need intensive care unit (ICU) admission because of severe respiratory failure, severe sepsis, or septic shock [32, 33] and CAP mortality in these patients remains very high, reaching near 50% [32]. A progressively higher incidence of severe CAP was reported in ICU, but the mortality rate had decreased by 18% over a 15-year period [34]. Data reporting on severity could be driven by reimbursement and, therefore, not represent a real increase in severity CAP. Patients who had been treated in the hospital for CAP have a clinically significant long-term poor survival when compared to matched controls. This increased post-discharge mortality is driven by pulmonary complications, new CAP episodes and cardiovascular

Table 1 CAP epidemiology and mortality worldwide

	Period	Type of study	Age (years old)	Overall CAP incidence per 1000 p/y	CAP incidence < 65 years per 1000 p/y	CAP incidence > 65 years per 1000 p/y	Admission (%)	In-hospital mortality (%)	Mortality (30 days, %)
Europe									
Spain [37]	2000–10	P	> 16	NA	NA	NA	82.4	NA	0.5
Europe [100]	2005–12	R	> 15	1.1–1.7	NA	14	2.5–4.3	NA	NA
UK [6]	2006–10	R	> 65	6.3–10.1	NA	NA	NA	NA	NA
Iceland [5]	2008–09	P	> 18	2.1[b]	1.37	9.02	NA	3	NA
Spain [101]	2009–13	R	> 18	4.63	2.5–5.8	5.4–36.9	NA	NA	NA
Germany [102]	2010–11	R	> 18	9.7	NA	NA	46.5	17.2	12.9
France [8]	2011–12	P	> 18	4.70	NA	6.70	7.0[a]	NA	0.30
USA									
USA (NYC) [103]	2000–14	R	> 18	4.8[b]	NA	NA	NA	7.9	NA
USA [9]	2010–12	P	> 18	2.5[b]	NA	NA	NA	2.0	NA
USA[a] [26]	2014–16	P	> 15	6.3	3.3	20.9	7.3	6.5	13.0
South America									
Latin America [47]	1970–08	Rw	> 50	2.9–29.0	NA	NA	11.4–45.3	7.6–9.8	12.4–13.1
Argentina[a] [11]	2012–15	P	> 18	1.8–7.0	2.3–11.9	10.9–29.4	NA	NA	12.1[c]
Asia									
New Zealand [104]	2002–03	R	> 15	8.6	NA	18.8	2.7–9.9	NA	NA
Japan[a] [105]	2011–13	P	> 15	16.9	4.5–11.8	42.3	5.3	11.5	NA
South Korea [106]	2011–14	R	≥ 19	3.1	0.9–3.6	16–48	NA	6.2	NA
Australia [17]	2011–13	R	> 19	2.5	NA	NA	NA	7.8	NA

Rw review article, *R* retrospective study, *P* prospective study, *NA* not available, *p/y* persons/year

[a] Reported as annual percentage

[b] Hospital cohort

[c] 14-day mortality

events, probably in the course of a persistent inflammatory response [32, 35].

CAP mortality reflects the enrollment of different patient populations in epidemiological studies as well as their methodology. Hospital and ICU admission criteria vary among different countries and hospitals, which hinders a comparison between them. Different admission criteria across countries, as well as the availability of ICU dedicated beds, technological and human resources could change reported mortality, as well as data regarding ICU admission. Other factors such as guideline adherence and quality of care could also reduce mortality [36]. This data is infrequently reported in epidemiological studies. Numerous patient risk factors and co-morbidities can hardly affect disease severity as well as the risk of death. Patient risk factors age, co-morbidities and immune status, together with microbiological pathogens and the absence of response to treatment also influence mortality [23].

CAP MICROBIOLOGY

Despite most of CAP episodes being caused by few microorganisms, several bacteria, viruses and fungi are recognized as causes of CAP. However, even when prospective studies were performed, less than half of patients presenting with CAP had a microbiologic diagnosis [9, 37–39]. Important variations are found according to patient severity and used diagnostic tools. The emergence of new diagnostic tests improved the recognition of pathogens compared with previous tests [40], not only for viruses but also for bacterial pathogens, allowing earlier directed therapy and antibiotic de-escalation. A higher rate of microorganism isolation was reported when newer diagnostic approaches and molecular techniques were used [39–41]. Some of these approaches are not widely available in clinical practice and their use remains controversial because no studies prove their outcome benefits and tests are costly. Moreover, antiviral agents are inactive against some viruses which precludes the utility of viral identification in clinical practice.

Streptococcus pneumoniae remains the most isolated bacterial pathogen in CAP worldwide in all treatment settings (outpatient, general ward and ICU) [37, 39, 40, 42–46]. *S. pneumoniae* resistance patterns remain different across countries. In recent studies, *Mycoplasma pneumoniae, Chlamydia pneumoniae* and *Legionella pneumophila,* which are well-established causes of CAP, have been isolated more frequently than before [19, 22, 47, 48] (Table 2). However, except for *L. pneumophila*, the diagnosis is difficult in clinical practice but could improve with multiplex PCR tests. *Haemophilus influenzae* account for 1.2–19% [49, 50] of all cases of bacterial CAP; however, this rose to around 50% in some studies [40]. *H. influenzae* is a major public health problem because of its increasing antimicrobial resistance. Given this resistance, specially to beta-lactams, *H. influenzae* was listed in the priority list of WHO antibiotic-resistant bacteria [51].

Unlike in other global areas, Gram-negative pathogens are also frequent pathogens (mostly *Klebsiella pneumoniae* and *Burkholderia pseudomallei*) in Asia. Meloidosis is a life-threatening infectious disease (caused by *B. pseudomallei*) that is endemic in South and Southeast Asia, northern Australia and China, peaking in the wet season. In some places, it is the third most common deadly disease after HIV and tuberculosis. Pneumonia is the most frequent presentation, with a mortality rate reaching 21% [52, 53], related to shock and bacteremia. Several cases are also reported in travellers returning from endemic areas [54, 55].

Even subject to some variations, generally methicillin-resistant *S. aureus* and MDR Gram-negative bacilli together cause CAP in approximately 5% of patients [56, 57], presenting even lower incidence in non-critically ill patients. While their empirical coverage is almost always unnecessary in CAP, in some areas and in patients with specific risk factors it could be considered; thus, inappropriate therapy is related to increasing mortality.

The precise role of viruses in CAP is not yet well established e.g. pathogens, co-pathogens, triggers or all-in-one. Respiratory viruses are isolated in up to one-third of patients with CAP [58–60]. However, it is not straightforward to

Table 2 Bacterial pathogens isolated in CAP

	Period	Type of study	Number	Bacterial diagnosis, %	*S. pneumoniae*	*H. influenzae*	*Staphylococcus aureus*	*Streptococcus* spp.[a]	*Moraxella catarrhalis*	*M. pneumoniae*	*C. pneumoniae*	*L. pneumophila*	Others
Poulose (Singapore) [107]	2003–05	P	80	30 (38.0)	10 (33.3)	1 (3.3)	1 (3.3)	1 (3.3)	2 (6.6)	0	0	1 (3.2)	14
Lui et al. (China) [41]	2004–05	P	1193	342 (28.7)	101(29.5)	62 (18.1)	NR	NR	NR	78 (22.8)	55 (16.1)	1 (0.3)	82 (24.0)
Johansson et al. (Sweden) [39]	2004–05	P	184	115 (62.5)	70 (60.1)	9 (7.8)	4 (3.5)	3 (2.6)	7 (6.1)	15 (8)	0	3 (2.6)	4
Shindo et al. (Japan) [49]	2010	P	887	475 (53.6)	152 (32)	92 (19.4)	88 (18.5)	23 (4.8)	32 (6.7)	11 (2.3)	31(6.5)	7(1.5)	39
Cao et al. (China) [50]	2010	P	197	81 (41.1)	9 (11.1)	1 (1.2)	0	1 (1.2)	0	63 (77.7)	0	0	7
Cillóniz et al. (Spain) [37]	2010–11	P	568	188 (33.2)	66 (35.1)	9 (4.8)	1 (0.5)	2 (1.1)	0	29 (15.4)	10 (5.3)	13 (6.9)	16 (8.5)
Jain et al. (USA) [9]	2010–12	P	2320	306 (13.2)	115 (37.6)	13 (4.2)	37 (12.1)	0	0	43 (14.1)	9 (2.9)	32 (10.4)	57 (18.6)
Seo et al. (South Korea) [108]	2010–16	R	1665	859 (51.6)	178 (20.7)	10 (1.2)	40 (4.7)	30 (3.5)	0	165 (19.2)	224 (26.1)	9 (1.0)	166 (19.3)
Dagaonkar et al. (Mumbai, India) [46]	2012	P	1000	580 (58.0)	133 (23.0)	5 (9.0)	0	0	35 (6.0)	29 (5.0)	64 (11.0)	17 (3.0)	297 (51.2)
Gadsby et al. (UK) [40]	2012–14	P	323	231 (71.5)	115 (49.8)	130 (56.3)	33 (14.3)	0	44 (19.0)	6 (2.6)	0	3 (1.3)	67 (29.0)
Aston et al. (Malawi) [109]	2013–15	P	459	278 (60.6)	98 (35.3)	0	2 (0.7)	0	0	6 (2.2)	2 (0.7)	6 (2.2)	20 (7.2)
Para et al. (North India) [44]	2013–15	P	225	153 (68)	61 (39.9)	0 (0.0)	12 (7.8)	0	0	13 (8.5)	10 (6.5)	33 (21.6)	31 (20.3)
Di Pasquale et al. (GLOBAL) [110]	2015	R	3702	869 (23.2)	268 (24.6)	75 (6.9)	188 (16.3)	0	0	0	0	31 (3.6)	309 (35.6)
Sahuquillo-Arce et al. (Spain) [42]	2016	P	4304	1526 (35.5)	933 (61.1)	42 (2.8)	41 (2.7)	0	0	51 (3.3)	50 (3.3)	110 (7.2)	141 (9.2)

Rw review article, *R* retrospective study, *P* prospective study, *NR* not reported

Table 3 Viral pathogens isolated in CAP

	Period	Number	Influenza viruses, *n* (%)	Rhinovirus, *n* (%)	Respiratory syncytial virus, *n* (%)	Parainfluenza viruses, *n* (%)	Other respiratory viruses, *n* (%)
Lui et al. (China) [41]	2004–05	1193	102 (8.5)	NR	NR	NR	0
Johansson et al. (Sweden) [39]	2004–05	184	14 (7.6)	12 (6.5)	7 (3.8)	7 (3.8)	0
Cao et al. (China) [50]	2010	197	9 (4.6)	2 (1.0)	2 (1.0)	4 (2.0)	7 (3.5)
Cillóniz et al. (Spain) [37]	2010–11	568	16 (2.8)	6 (1.1)	1 (0.2)	1 (0.2)	1 (0.2)
Jain et al. (USA) [9]	2010–12	2259	132 (5.8)	194 (8.6)	68 (3.0)	67 (3.0)	173 (7.7)
Seo et al. (South Korea) [108]	2010–16	1665	15 (0.9)	2 (0.1)	2 (0.1)	2 (0.1)	6 (0.4)
Gadsby et al. (UK) [40]	2012–14	323	23 (7.1)	41 (12.7)	4 (1.2)	11 (3.4)	19 (5.9)
Aston et al. (Malawi) [109]	2013–15	459	40 (8.8)	17 (3.7)	8 (1.7)	17 (3.7)	98 (21.6)
Para et al. (North India) [44]	2013–15	225	13 (5.8)	0	0	0	0 (0.0)
Di Pasquale et al. (GLOBAL) [110]	2015	3050	0	0	7 (0.2)	0	11 (0.4)

NR not reported

assume that the presence of virus isolates in nasopharyngeal swabs (as performed in most studies) is sufficient to explain CAP pathogenesis. Almost all studies (Table 3) using polymerase chain reaction (PCR) reported influenza, rhinovirus and respiratory syncytial virus (RSV) as the commonest isolated, but whether they are true pathogens remains debatable. Metapneumovirus was first described as a pathogen in children; however, it also infects adults, but the incidence is lower than in children [61]. Adults can carry the virus asymptomatically. However, it was recognized as a single CAP pathogen in 4% of patients in the USA [9] and recently had been implicated in severe CAP [61]. Similarly to other viruses, metapneumovirus appears to have a seasonal variation with a peak after influenza season.

Microbiology remains of utmost importance given that it has a significant prognostic impact.

UNMET CLINICAL NEEDS

CAP unmet clinical needs set priorities for research topics in CAP therapy and prevention through vaccines, that are, in our opinion, important to be perform in the next few years,

Table 4 Unmet clinical needs in CAP

Therapy
What time is acceptable to start antibiotics in patients with CAP?
Why is evidence of short duration antibiotic therapy in CAP not applied in clinical management?
Which patients should be treated with antiviral therapy in CAP?
Should antiviral therapy be used empirically during influenza seasonal epidemics or all year?
Could PK/PD interventions change the outcomes in severe CAP?
In non-severe CAP might new oral antibiotics be directed to once-daily dosages?
What is the role of tetracyclines in CAP treatment?
In severe CAP what is the best drug on top of beta-lactam therapy: macrolide or quinolone?
Adjunctive therapies
Which patients will benefit from steroid therapy in CAP?
What are the best steroid, steroid dose and duration in CAP?
In patients with CAP presenting with high inflammatory response, can steroid therapy improve hard outcomes?
How should viral infection be excluded before steroid treatment?
Can steroids and macrolides have an addictive anti-inflammatory effect?
Is PCV13 superior to PPV23 in invasive pneumococcal disease and pneumococcal CAP?
Prevention
Which is the best scheme/schedule of anti-pneumococcal vaccination?
Is vaccine efficacy equivalent in immunocompetent and immunosuppressed patients?
Is adult pneumococcal vaccination cost-effective in settings with high childhood vaccination rates?
Will vaccines directed to *S. pneumoniae* virulence factors be more efficient than current ones?
Epidemiology
New randomized controlled trial (RCT) to study performance of new drugs in patients with severe CAP (PSI > 120, PORT class V)
Which is the epidemiology of lethal CAP?
What is the real burden of morbidity and mortality after CAP?
How should microbiologic surveillance be performed in a global way?

based on currently available evidence. The most important challenges in clinical research of CAP are listed in Table 4.

Antibiotic Therapy

In the last decade, many efforts were made to develop new drugs, resulting in newly approved antibiotics listed in Table 5. However, new antibiotics were often being developed to improve their activity against several MDR microorganisms, which are, as previously shown, uncommon in CAP. Most of these trials focused on patients with non-severe CAP requiring hospitalization [62–68], excluding severely ill patients (or ICU patients), so recommendations for these groups of patients are

Table 5 New antibiotics for CAP treatment

	Reported severity of patients included in trials	Dose and posology
Ceftobiprole	All hospitalized patients; PORT risk class V: 1.7% of population study[a]	500 mg, iv, 8/8 h, 2 h infusion
Ceftaroline	Only PORT risk class III or IV (not admitted to ICU on recruitment)	600 mg, iv, 12/12 h
Omadacycline	PORT risk class II, III or IV	100 mg, iv, 12/12 h for 2 doses, followed by 100 mg, iv, daily, or 300 mg, orally, daily
Delafloxacin	PORT risk class II–V, excluding patients admitted to ICU (not yet published)	300 mg, iv, 12/12 h or 450 mg, orally, 12/12 h
Solithromycin	PORT risk class II–IV in both trials	800 mg orally (or 400 mg iv), on the first day followed by 400 mg orally or iv, daily
Lefamulin	(a) PORT risk class $\geq$ III, excluding mechanically ventilated; in PORT class III–V, not mechanically ventilated; (b) PORT risk class II–IV	150 mg, iv, 12/12 h or 600 mg, orally, 12/12 h

PORT Pneumonia Patient Outcomes Research Team, *iv* intravenous
[a] Ceftobiprole arm 1.2% (4/314) and comparator arm 2.2% (7/329)

derived from studies without their representation. It is an important limitation for the widespread use of new antibiotics, in spite of drug usage specificities in critically ill patients. Studies are needed in more severely ill patients. RCTs showing superiority instead of "non-inferiority" are needed to show a clear advantage of new drugs. In the period after introduction of new antibiotics, microbiological resistance surveillance remains essential because of new antibiotic pressure among pathogens, which could lead to resistance. Long-term side effects should also be studied.

Adjunctive Therapies

Several therapies have been tested to improve CAP outcomes using different strategies, to target innate immunity and adaptive immunity, as well as other immunomodulatory or anti-inflammatory drugs. For the purpose of this review we focus on adjunctive therapies to steroids and macrolides that are clinically available and the subject of many studies. Difficulties in showing an impact on hard outcomes, and difficulties in properly identifying the patients that will benefit more of them, impair the use of adjunctive therapies. Furthermore, as these therapies focus mainly on the inflammatory response, long-term outcome studies should be performed to analyze how they modulate long-term mortality that is related to chronic inflammatory status.

Steroids

The use of steroid therapy in patients with bacterial CAP remains uncertain, mainly because of the lack of knowledge about which phenotypes of disease and patient groups will have greater benefits from this therapy.

Inflammatory response contributes to CAP mortality. Steroid therapy reduces the inflammatory response and is therefore believed to improve outcomes in patients with CAP . However, this assumption remains controversial because of conflicting results regarding mortality [69–73]. Although it is likely to enhance patient performance, the published positive results focused on soft outcomes (reduction of treatment failure, length of stay, progression to acute respiratory distress

syndrome, radiological progression and time to clinical stability) [69–73]. Steroid treatment depending on high inflammatory response should also be retested addressing hard endpoints [74] because the previous published RCT used radiological improvement as a primary outcome. The only study that established mortality as the primary outcome [75] has not yet been published. Precise identification of patients that will benefit from steroids is critical, given that these drugs have important side effects. Steroids have the potential to reduce survival in viral respiratory infections. The ideal method to convincingly exclude viral infection before steroid therapy initiation should also be addressed. For that, new studies are needed in specific populations (i.e. studying separately severe and non-severe CAP) to improve the body of evidence about steroid usage in CAP.

Macrolide Therapy

Macrolide therapy is used frequently in respiratory diseases for its antimicrobial activity and anti-inflammatory effects. Several in vitro and in vivo studies proved this ability through a reduction in pro-inflammatory interleukins and improved levels of anti-inflammatory ones, as well as the ability to reduce polymorphonuclear neutrophil (PMN) recruitment and decrease reactive oxygen species [76–80]. The clinical meaning of these findings remains controversial because, for now, there is no randomized clinical trial confirming the superiority of therapies containing macrolides regarding mortality [81, 82]. However, observational studies [83–86] showed consistently improved outcomes in invasive pneumococcal disease in severely ill patients (i.e. invasively ventilated and under vasopressor treatment). Some guidelines [87–90] recommend use of macrolides in combination therapy with beta-lactams as first-line therapy in CAP, either in ICU and non-ICU patients. Those recommendations were mainly driven by observational studies that are subject to bias. Evidence from recent RCTs [91], failed again to show the advantages of this approach in non-critically ill patients that had never been clearly shown. The generalized use of macrolides has the potential to promote antibiotic resistance, so until an RCT shows evidence of benefit macrolides should be judiciously used in non-critically ill patients, whereas macrolides are associated with QTc interval prolongation, gastrointestinal events and drug interactions.

Vaccination

Pneumococcal vaccination [92], where the vaccination rate is higher, contributes to pneumococcal vaccine-type disease reduction. Data regarding herd protection is not consensual, but its disparity could be explained by the different time intervals between generalized vaccination and studies [93, 94]. Further, vaccine introduction also leads to serotype shifting; meanwhile, no effects in resistance patterns were noted [95]. Several efforts were made to develop a vaccine to prevent pneumococcal infection resulting in two available vaccines: pneumococcal polysaccharide 23-valent (PPV23, contains capsular polysaccharides of 60% of serotypes causing disease in adults) and pneumococcal conjugate 13-valent (PCV13, stimulates antibody production against 28–42% of serotypes causing disease, varying according different geographical areas). For both, vaccine efficacy has been proven for invasive pneumococcal disease [96, 97]. Only PCV13 has been clearly associated with the prevention of non-invasive and invasive pneumococcal community-acquired pneumonia (CAPiTA trial [97]) regarding vaccine-targeted serotypes. In different countries, vaccine indications vary, some based on believing that PCV13 could boost immunity created by PPV23 (when previously administered) [98]. It is controversial whether PCV13 is superior to PPV23, because comparative trials are lacking. New outcomes should also be determined for invasive pneumococcal disease and pneumococcal CAP, as well as all-cause mortality and pneumococcal CAP-related mortality. The definition of immunosuppressed patients also varies according to different studies, which impairs the process of studying real immunosuppressive risk factors for pneumococcal infection.

Table 6 Pneumococcal vaccine indications and described vaccine efficacy

	Pneumococcal polysaccharide 23-valent	Pneumococcal conjugate 13-valent
Serotypes included	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F and 33F	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F and 23F
Vaccine efficacy [97]		
IPD	60.0%	75.0%
PCAP	63.8%	45.6%
Vaccine indications		
Immunocompromised	HIV, nephrotic syndrome, chronic kidney disease, immunodeficiency (congenital and acquired), metastatic cancer, lymphoma, leukaemia, Hodgkin disease, multiple myeloma, transplanted, immunosuppressed	
	Asplenia (functional and anatomical): congenital, acquired and haemoglobinopathies	
Immunocompetent	Age > 65, cochlear implant, cerebrospinal fluid leak, medical co-morbidities[a]	

IPD invasive pneumococcal disease, *PCAP* pneumococcal community-acquired pneumonia
[a] (Dependent of country policy) chronic heart, lung or liver disease, diabetes mellitus, smoking, alcohol use disorder

While in immunocompromised patients indications for vaccination are well established (Table 6), in other groups evidence is less clear, allowing different recommendations in different countries. Pneumococcal vaccine calendar, administration of one or both vaccines [99], should be further elucidated in new studies. After introduction of vaccines, pneumococcal microbiology in CAP moved to serotypes that are not included in vaccines [95]. New vaccines immunizing widely for other serotypes will be valuable, as well as other vaccine approaches targeting *S. pneumoniae* virulence factors. Cost-effectiveness of vaccination in adults should be evaluated to analyze whether high child pneumococcal immunization could modify its cost-effectiveness in adults and the elderly.

CONCLUSION

The large body of evidence discussed has exposed the high incidence and mortality of CAP, usually related to older age and co-morbidities. CAP microbiology had been changed because new diagnostic tests have turned viruses into the most identified pathogens, while their role in pathogenesis is not fully explained. Adjunctive therapies should remain part of CAP tailored management. Vaccines should remain the backbone of bacterial CAP prevention. Further studies are needed to improve outcomes in patients with CAP.

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