Current Concepts of Severe Pneumococcal Community-acquired Pneumonia

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Introduction

Community-acquired pneumonia (CAP) is a major health problem, even in developed countries, being the leading cause of death due to infectious diseases in the USA [1]. CAP has a wide clinical spectrum of severity: up to 80% of patients are successfully managed in primary care, but 1% of patients with CAP are classified as having severe disease, needing intensive care unit (ICU) admission, with 20–50% dying despite all available support and treatment options being utilized. *Streptococcus pneumoniae* is the most common cause of CAP, enclosing the subset group of patients having severe disease [2]. Moreover, bacteremia is not uncommon in pneumococcal CAP (20%) and has been associated with increased severity and mortality compared with non-bacteremic pneumonia [3].

The morbidity and mortality of severe pneumococcal CAP have remained essentially unchanged despite emergence of new antimicrobial options and improvements in critical care medicine. Our failure to improve the outcome from pneumococcal CAP may in part be due to the aging population and the increased burden of comorbid illnesses including larger numbers of immunosuppressed patients due to chemotherapy or human immunodeficiency virus (HIV); however our basic understanding of why people die from this disease is still poor. Several prognostic factors are known to be associated with adverse outcome, however morbidity and mortality are more likely determined by the result of complex interactions between the host's defenses, the virulence of the infecting strain and possibly the timing and choice of

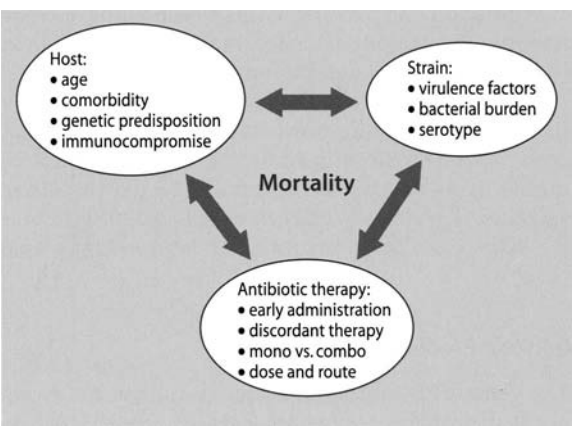

Fig. 1. Interaction of factors influencing survival. From [58] with permission

antibiotic therapy, than the presence or absence of one or more risk factors. The knowledge of these interactions could also explain the variability in the clinical presentation of pneumococcal CAP (Fig. 1).

Microorganism-host Interactions

Age and Comorbidity

Although there is a great variability in studies reporting the influence of age on mortality, there is no doubt that it is one of the main prognostic factors in CAP. Even in the pre-antibiotic era, age was a significant predictor of mortality [4], and the Applied Physiology And Chronic Health Evaluation (APACHE) scores have a significant weighting for age [5]. A meta-analysis suggested that each 10-year age increment represents an increase of 5% in the likelihood of death (OR = 1.05 95% CI 1.01 – 1.09) [6]. Moreover, demographic variables (mainly age) constitute the first step of one of the more commonly used outcome prediction rules in CAP [7].

Nevertheless, it is noteworthy that advanced age (>65 years old) was an independent and protective factor (OR = 0.35) associated with early failure in a cohort of 1383 patients with CAP [8]. This finding supports the hypothesis that the main cause of death in old patients is related more to decompensation of underlying comorbidities or to their deteriorated baseline status than to the severity of the acute inflammatory process. This study [8] also demonstrated that patients at risk of early clinical failure have more severe pneumonia at admission (multilobar pneumonia, pneumonia severity index [PSI] >90 at admission) suggesting that in those early failures despite adequate antibiotic coverage, a genetic mediated predisposition could play an important role (see below).

Nearly all studies in CAP have reported increased mortality in patients with baseline comorbidities, although the influence of each specific comorbidity varies from study to study. Neurologic and neoplastic comorbidities were the most powerful predictors of increased mortality in one meta-analysis [6]. The influence of chronic obstructive pulmonary disease (COPD) is particularly controversial, with a recent study suggesting it may be a protective factor [9], whereas in others it constitutes a risk factor for mortality [10]. Further studies are needed to address this issue further.

Another controversial issue is the impact of vaccination status. The 23-valent pneumococcal polysaccharide vaccine (Pneumovax, Merck) is not 100% efficacious in preventing invasive pneumococcal disease and did not prevent non-bacteremic pneumonia in a recent study. [11], but in another study, focused on elderly people, the 23-valent vaccine prevented pneumococcal pneumonia (with or without bacteremia) and decreased the rates of overall pneumonia and of mortality due to pneumonia in this subset of patients [12]. On the other hand, pneumococcal conjugate vaccines (7-valent, 9-valent and 11-valent) provide adequate coverage for children <2 years old against serotypes most frequently associated with penicillin-resistance [13].

Genetic Predisposition

The genetic risk for severe pneumonia is usually underestimated in clinical practice, but it is probably the major factor in unexpected mortality in young and previously

healthy patients and in the variability in clinical presentation in patients with similar baseline status and same infecting strain.

Briefly, when the host recognizes the presence of foreign antigens through specific antigen recognition pathways (predominantly the innate but also the acquired immune system), a pro-inflammatory reaction is initiated, in order to eradicate the infecting strain. At the same time, an anti-inflammatory reaction is mandatory to counteract potential deleterious effects of pro-inflammatory mediators. An imbalance between these two reactions can lead to a deficient response to infection. Thus, an excessive pro-inflammatory response, or a deficient anti-inflammatory response, could lead to septic shock or secondary organ damage, and conversely, a deficient pro-inflammatory or enhanced anti-inflammatory reaction could lead to persistent infection [14]. The main pro-inflammatory cytokines so far identified as being important in CAP are tumor necrosis factor-alpha (TNF-α), lymphotoxin-α (LTA), interleukin (IL)-1 and 6, and the principal anti-inflammatory mediators appear to be IL-10 and IL-1 receptor antagonist (IL-1ra).

The host response against pulmonary infection is represented by the innate and adaptive components of the immune system. The innate immune system is considered as the first line of defense against invading microorganisms. The classical and alternate complement pathways play a key role in the innate response, but there are other pathways that contribute to the opsonization of microorganisms. One of these is the lectin pathway, mannose-binding lectin (MBL) being one of the opsonins. Several genetic polymorphisms (mutant alleles with a frequency in the general population of $>1\%$) are associated with a low plasma concentraion of MBL. In a case-control study, Roy and co-workers [15] found that homozygosity for several of these alleles is associated with very low levels of serum MBL, and indeed, with inadequate opsonic function. Consistent with the reduction in function being clinically relevant, the low-function associated mutations of MBL were over represented (OR= 2.59) in patients with invasive pneumococcal disease. Moreover, polymorphisms associated with deficiency of MBL in serum have been associated with an increased risk of developing systemic inflammatory response syndrome (SIRS) and progression of infection to sepsis and septic shock [16].

Toll-like receptors (TLRs) are also part of the innate immune defense and recognize structurally conserved pathogen-associated molecular patterns (PAMPs). TLR-2, and probably TLR-4, are involved in the host innate immune response to pneumococcal infection in mice models [17]. In humans, deficient TLR-mediated cytokine production was associated with recurrent pneumococcal bacteremia in a child [18].

Surfactant proteins are one of the most important molecules in the early stage of pulmonary infection. Surfactant-D (SP-D) seems to have a special ability to interact with several serotypes of pneumococci, clearing the microorganism from lungs and upper respiratory airways and delaying its appearance in bloodstream. Recently, Quasney and co-workers demonstrated that carriage of the C allele at the SP-B + 1580 locus was associated with acute respiratory distress syndrome (ARDS), septic shock, and the need for mechanical ventilation in a cohort of 402 adults with CAP [19].

TNF-α is one of the most extensively studied mediators, due to its critical role in the pro-inflammatory response against infection and its high degree of polymorphism, especially within the promoter region of the gene. The main problem in establishing a causative relationship between individual(s) genotypes and a TNF-α secretor pattern, and indeed outcome, is that there are several loci in linkage associ-

ation in the same region (chromosome 6) that could act as an etiologic factor or merely be a marker for other polymorphisms not just in TNF-α but in one of the many key inflammatory proteins located nearby. One of the best studied polymorphisms is TNF-308. This polymorphism is associated with two patterns of secretion. Carriage of A allele is associated with high TNF-α levels and is associated with septic shock [20], even in CAP [21], whereas polymorphisms associated with low TNF-α levels (G alleles in locus TNF-α-308) have a protective effect against the development of septic shock, but a trend to a greater risk of developing respiratory failure has been documented [21]. As mentioned earlier, another polymorphism in linkage disequilibrium with TNF-α-308 is the LTA +250 polymorphism. Thus, carriage of A alleles of LTA 250 is also associated with high-TNF levels, and inversely, carriage of G alleles is associated with low blood TNF levels, and both loci (LTA +250 and TNF-α-308) are in linkage disequilibrium. Similarly, the same authors reported more recently an association of carriage of heat shock protein (HSP) 70-2+1267 AA genotype and risk of septic shock in patients with CAP, with a stronger association than the LTA 250 genotype described earlier [22].

Anti-inflammatory cytokines are able to counterbalance harmful effects of the inflammatory response. In pneumococcal disease, IL-10 is one of the best studied anti-inflammatory mediators. In humans, the IL-10-1082 gene promoter polymorphism is associated with high IL-10 inducibility (G genotype) [23]. Recently Schaaf and colleagues [24] found that IL-10-1082 G>C was associated with an increased risk of pneumococcal septic shock.

The Virulence of the Infecting Pneumococcal Strain

The pathogenicity of pneumococci has been attributed to several components. The polysaccharide capsule was considered the primary virulence factor of *S. pneumoniae* because although pneumococcus exists in encapsulated and unencapsulated forms, only encapsulated strains have been recovered from clinical specimens. Classical studies carried out by Avery and Dubos [25] demonstrated that loss of the capsule is accompanied by a 100,000-fold reduction in the virulence of pneumoccoci. On the basis of differences in capsular polysaccharide structure, pneumococci can be divided into 90 serotypes, but less than 30 serotypes account for up to 90% of invasive disease in humans. Recent epidemiological studies report the dominant role of individual serotype in determining invasiveness. Brueggemann et al. [26] compared the distribution of invasive isolates with carriage isolates and showed that the potential of pneumococci to cause invasive disease differs by serotype. These authors observed that serotypes 6B, 19F, and 23F are commonly carried but have low invasiveness. Other serotypes, such as serotype 1, 5 or 7F, are rarely carried but they are common causes of invasive disease in some countries due to their high invasiveness. Other authors [27] have reported an association between capsular serotype and mortality; serotypes 3, 6B, and 19F were associated with higher mortality (25% vs 0%) when compared with serotypes 1 and 7F. A recent study has demonstrated that pneumococcal clones of serotype 1 and 7F, primarily infect previously healthy individuals and behave as 'primary pathogens' [28]. In contrast, other clones belonging to serotypes with a lower potential for causing invasive disease, behaved more like 'opportunistic pathogens'. In the majority of cases, infections with such clones cause disease in patients with underlying disease, and are associated with more severe disease.

Current studies suggest that certain pneumococcal proteins contribute significantly to the virulence of individual strains. These proteins are involved in direct interactions with host defense mechanisms. These proteins include hyaluronate lyase (Hyl), pneumolysin, neuraminidase A (NanA), neuraminidase B (NanB), major autolysin (LytA), choline binding protein A (CbpA), pneumococcal surface antigen A (PsaA), and pneumococcal surface protein A (PspA). Development of antibodies against some of these proteins may be a promising approach for use in a future vaccine and have recently been investigated [29]. The antigens that reduce virulence are the best candidates for vaccine development, such as pneumolysin, PspA, and LytA.

- Pneumolysin is a 53 kDa protein produced by all *S. pneumoniae* isolates. The virulence properties of pneumolysin are directly dependent on the action of autolysin. The role of pneumolysin is crucial particularly in the early stages of pneumococcal infection. Pmeumolysin has the ability to lyse cell membranes, activate complement, and stimulate the production of inflammatory cytokines, such as TNF-α and IL-1β [30]. Other studies have reported that low concentrations of pneumolysin are able to inhibit neutrophil and monocyte respiratory response, chemotaxis, bactericidal activity, and production of lymphokines and inmunoglobulins [31]. The cytolytic properties of pneumolysin cause damage to ciliated bronchial epithelial cells, alveolar epithelial cells, and pulmonary endothelium. The result is that the ability of ciliated bronchial cells to clear mucus and particles from the lower respiratory tract is reduced, facilitating the bloodstream spread of infection [32]. In a recent study in a mouse model, Witzenrath and coworkers demonstrated that pneumolysin may play a central role in early acute lung injury (ALI) in pneumococcal pneumonia by causing impairment of pulmonary microvascular barrier function and severe pulmonary hypertension [33].
- Pneumococcal surface protein A (PspA) exhibits structural and antigenic variability between different pneumococcal strains, but is present in most pneumococcal clinical isolates [34]. Hammerschmidt et al. [35] identified PspA as a lactoferrin-binding protein and demonstrated that PspA plays an important role in enabling iron acquisition by pneumococci. The function of PspA appears to be protection against the host's complement system [36]. Briles et al. [37] observed biological evidence of the anti-complementary properties and have shown that PspA reduces the complement-mediated clearance and phagocytosis of *S. pneumoniae.*
- Autolysin is responsible for cell wall lysis [38]. Cell wall degradation has significant physiological consequences. Autolysin activity generates cell-wall breakdown products, which are highly inflammatory and allows the release of intracellular toxins (e.g., pneumolysin).

Pneumococci contain many other proteins that could contribute to pathogenicity, but their role has not yet been completely established. Potential key proteins include hyaluronidase adhesins, and, especially, neuraminidase A and B. Their role in the development of upper and lower infection and sepsis has been emphasized in a recent study [39].

Penicillin-binding proteins (PBPs) are another group of virulence determinants. PBPs are a group of proteins located in the cell wall of pneumococci, and are the key proteins in the determination of penicillin-resistance. It has been hypothesized that pneumococci with reduced susceptibility to penicillin are less invasive than wild strains. In an experimental study in a mouse model, Magnusdottir and coworkers demonstrated that resistant strains had a significantly reduced ability to persist at

the infectious site, and to some extent also to induce infections, compared with fully susceptible strains [40]. In the clinical setting, there are several studies showing that invasive isolates are much more likely to be penicillin sensitive that non-invasive isolates [41]. It seems that the acquisition of resistance is counterbalanced by a 'biological cost' in terms of virulence.

Antibiotic Therapy

None of the conditions described above can be modified in patients admitted with severe pneumococcal pneumonia. Until immunomodulatory therapies appear as a true alternative treatment, genetic markers are interesting adverse prognostic factors but have no current role in clinical management. Currently, the efforts of the physician are directed towards optimizing supportive therapies and choosing the appropriate empiric antibiotic treatment.

In the antibiotic treatment of pneumococcal pneumonia, there are currently two important unresolved questions: The impact of discordant antibiotic treatment on mortality and the hypothesis that dual therapy could improve prognosis.

The Impact of Discordant Therapy on Mortality

The discovery in South Africa of penicillin resistant pneumococci [42] posed the question whether this acquisition of resistance would worsen the prognosis of patients with pneumococcal disease treated with beta-lactams. The answer to this question is not trivial, because it reflects the degree of correlation between the cut-off points used in the laboratory to define categories of susceptibility for pneumococcal strains and the clinical course in patients receiving those antibiotics considered sensitive or resistant *in vitro*.

The impact of penicillin resistance on outcome has been extensively investigated by a great number of experts. The most frequently employed definition of discordant therapy in these earlier studies included intermediate and resistant infecting strains. Early studies seem to suggest that the level of resistance had little effect on the outcome of pneumococcal pneumonia [43]. Surprisingly, few studies have recorded the administered empiric antibiotic therapy, dose, route, and interval of administration, and the definition of discordant therapy has been based only on the minimum inhibitory concentration (MIC). Furthermore, given the complexity of the pharmacokinetics and pharmacodynamics of antibiotic therapy (peak serum concentrations, time above MIC, mechanisms of resistance of different antibiotics) categorical classification based on an arbitrary MIC cut-off for the administered antibiotic seems simplistic [44]

One of the most important studies about this point analyzed the factors affecting mortality in a cohort of patients with pneumococcal pneumonia during the period 1995–1997. More than 5800 patients were included in the study and the authors found that mortality was significantly associated with strains with a penicillin MIC of 4 μg/ml or greater or a cefotaxime MIC of 2 μg/ml or greater, when controlled for underlying conditions and when deaths within the first 4 hospital days were excluded. The reason early deaths were excluded was for the known lack of any impact of antibiotic therapy early in the disease course [45]. Given the results of this and other studies, and following the recommendations of a panel of Centers for Disease Control and Prevention (CDC) experts, in 2002 the National Committee for

Table 1. MIC interpretive standards (in μg/mL) for non-meningeal pneumococcal infections according to the 2002 breakpoints [46]

Group	Antimicrobial agent	MIC (μg/ml) Interpretive standards		
		Susceptible	Intermediate	Resistant
Penicillins	Penicillin	≤ 0.06	0.12–1	≥ 2
	Amoxicillin	≤ 2	4	≥ 8
	Amoxicillin-clavulanate	≤ 2/1	4/2	≥ 8/4
Cephalosporins (parenteral)	Cefuroxime	≤ 0.5	1	≥ 2
	Cefotaxime or ceftriaxone	≤ 1	2	≥ 4
	Cefepime	≤ 1	2	≥ 4
Cephalosporins (oral)	Cefuroxime axetil.	≤ 1	2	≥ 4
	Cefaclor	≤ 1	2	≥ 4
Carbapenems	Imipenem	≤ 0.12	0.25–0.5	≥ 1
	Meropenem	≤ 0.25	0.5	≥ 1
Glycopeptides	Vancomycin	≤ 1	–	–
Macrolides	Erythromycin/Clarithromycin	≤ 0.25	0.5	≥ 1
	Azithromycin	≤ 0.5	1	≥ 2
Fluoroquinolones	Levofloxacin	≤ 2	4	≥ 8
	Moxifloxacin/Gatifloxacin	≤ 1	2	≥ 4
	Grepafloxacin/Sparfloxacin	≤ 0.5	1	≥ 2
Lincosamides	Clindamycin	≤ 0.25	0.5	≥ 1

Clinical Laboratory Standards (NCCLS) raised the breakpoints for susceptibility for pneumococcal non-meningeal infections (Table 1) [46].

Once the breakpoints had been changed, several studies tried to address whether this change led to a better correlation between susceptibility of strains and mortality. In a multicenter study, Yu and co-workers [47] included 844 patients with bloodstream pneumococcal infection from various sites, and found that neither the resistance to penicillin, nor initial discordant therapy were associated with mortality when non-meningeal infection was analyzed. Only discordant therapy with cefuroxime was related to mortality, and the authors argued that the most commonly employed dose (750 mg every 12 hours) was suboptimal to maintain serum levels above MIC for more than 50% of the dosing interval. Of note, in this study patients with several sources of infection were included, and only patients receiving monotherapy were included in the analysis of discordant therapy related to mortality. Interestingly, in a study including 100 patients with bacteremic pneumococcal pneumonia an excess mortality for those receiving discordant therapy was found [10].

What are the reasons for these discrepancies? Probably, most studies are underpowered because less than 15% of patients received discordant therapy, and we expect mortality to be less than 2% in Pneumonia Outcome Research Team severity index (PORT) I to III classes, which represents the vast majority of patients. It is likely that discordant therapy will have a stronger effect in PORT IV/V classes. Moreover, although the resistance and implications of discordant therapy with beta-lactams have been the most extensively studied, discordant therapy including macrolides has been demonstrated as being associated with therapeutic failure [48], and

therapeutic failure with non-pseudomonal fluoroquinolones [49] has also been reported. Are the implications of discordant therapy the same with all groups of antibiotics? The answer to this question is crucial to determine whether the current breakpoints correlate with clinical outcome.

Monotherapy or Dual-therapy for Bacteremic Pneumococcal Pneumonia

The current guidelines of several societies recommend the use of a combination of a beta-lactam plus a macrolide or monotherapy with a respiratory fluoroquinolone (levofloxacin, moxifloxacin) to treat hospitalized patients with CAP. In patients with severe CAP admitted to an ICU, combination therapy (beta-lactam/macrolide) is more usual, in part due to the lack of ventilated patients in randomized control trials evaluating fluoroquinolones as monotherapy. Some investigators have evaluated the outcome of patients receiving combination versus monotherapy in pneumococcal CAP in particular. Combination therapy has been suggested to have a favorable influence on outcome, but prospective, randomized controlled studies are lacking.

Mufson and Stanek [50] performed a retrospective study including 423 patients with bacteremic pneumococcal CAP over a study period of 20 years. The main results were that combination therapy including macrolides was associated with lower case-fatality rates. Nevertheless, their conclusions are weakened by important limitations, because information about sensitivity was not provided and adjustment for severity was not performed.

Waterer and co-workers [51] also retrospectively studied 235 patients with pneumococcal bacteremic CAP. Their hypothesis was that combination therapy with more than one effective antibiotic would be superior to monotherapy in bacteremic pneumococcal pneumonia. To exclude a potential influence of discordant therapy, patients with immunocompromise or strains resistant to prescribed therapies were excluded. Moreover, the group of patients receiving three or more antibiotic agents was excluded from analysis, due to substantially greater severity of disease. Dual empiric therapy was associated with higher survival rates when PSI >90, and the benefit was confirmed in a multivariate analysis (adjusted OR=6.4; 95% CI 1.9–21.7). Nevertheless, possibly due to the wide range of antibiotic regimens prescribed, it was not possible to demonstrate whether one concrete regimen could improve outcome.

More recently, Martinez et al. [52] retrospectively analyzed 409 patients with pneumococcal bacteremic CAP, during a study period of 10 years; 238 patients received a regimen containing a macrolide, whereas 171 did not. In the stepwise logistic regression analysis, lack of prescription of a macrolide in the initial antibiotic empiric therapy was associated with mortality (when adjusted for shock). Conclusions should be interpreted with caution due to the retrospective design of the study and the differences in the groups Thus, patients in the macrolide group were more likely to experience shock, whereas patients in the non-macrolide group were more likely to have a poorer baseline status: more comorbidities, more ultimately or rapidly fatal underlying disease, higher prior antibiotic exposure, steroid use, antineoplastic therapy and more likely to be infected with resistant strains.

Baddour et al. [53] analyzed the influence of combination antibiotic therapy in patients with pneumococcal bacteremia. Although prospectively conducted, the study was not a randomized controlled trial. Eight hundred and fourty-four patients with pneumococcal bacteremia from several sites (793 with pneumonia) were included, and 592 were evaluable for analysis of monotherapy versus combination

therapy. The 14-day mortality was not significantly different for all patients pooled together, but among critically ill patients, defined according to a Pitt bacteremia score >4, combination therapy was associated with lower mortality (23.4 versus 55.3%, $p<0.01$).

Conversely, Harbarth et al. [54] reported the lack of influence of mono versus combination empiric therapy at admission in a subset of 107 patients with monobacterial pneumococcal sepsis. Nevertheless, this study presents certain differences with respect to the others mentioned: first, immunocompromised patients were excluded; second, only six patients received fluoroquinolone-containing regimens; and most importantly, only a proportion of these patients had bacteremia. When only bacteremic patients (n=75) were analyzed, no statistical differences in short-term mortality were found, but the small sample size is clearly underpowered.

More recently, Dwyer et al. [55] found no effect of the addition of a macrolide to a beta-lactam based empiric regimen in case fatality-rate in a cohort of 340 patients with bacteremic pneumococcal pneumonia studied retrospectively. Finally, Rodriguez et al. (unpublished data), using a Cox proportional hazard model, adjusted for severity-of-illness, have recently documented that 28-day ICU mortality rate is significantly reduced in patients admitted to the ICU by CAP with shock, if they receive initial combination therapy.

Prospective controlled trials to address this question have been conducted, but the results have not yet clarified whether combination therapy is superior. Finch et al. [56] compared treatment with moxifloxacin versus amoxicillin-clavulanate with or without clarithromycin in patients with CAP. Mortality in both groups was equivalent but overall mortality was only 4.8%, meaning that the study was underpowered to identify differences in mortality. Similarly, the study of Frank et al. [57] compared levofloxacin versus ceftriaxone plus a macrolide in a cohort of 236 patients with CAP. No differences in mortality were found, but overall mortality was <2% in both arms.

In summary, several retrospective studies have suggested a superiority of combination therapy in comparison with monotherapy in severe pneumococcal pneumonia, but these results have not yet been supported by randomized controlled trials focused on severe pneumonia. Whether these findings can be extrapolated to non-bacteremic patients or in a full cohort of etiologies remains uncertain. Clearly, further studies are needed that focus on PORT IV-V class pneumonia, if endpoints are related to survival. Future studies should compare conventional dual therapy (such as beta-lactam plus macrolide) to monotherapy with newer fluoroquinolones.

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