Severe community-acquired pneumonia: a paradigm shift toward precision diagnostics, microbiology, and targeted management

Ignacio Martin-Loeches[a,b,c], *Marcos I. Restrepo*[d,e] *and Antoni Torres*[f]

Purpose of review
Severe community-acquired pneumonia (sCAP) remains one of the most lethal infectious syndromes in critical care, with mortality remaining persistently high despite decades of antimicrobial and supportive care advances. This review appraises recent developments in diagnostics, microbiology, and host-response biology, and advocates for a fundamental shift toward precision-driven management.

Recent findings
High-resolution molecular diagnostics have exposed the true complexity of sCAP, revealing a substantial viral burden and a polymicrobial ecosystem that challenges traditional pathogen-centric models. Yet, this diagnostic revolution has failed to translate into meaningful antimicrobial stewardship, reflecting a persistent disconnect between detection and decision-making. At the same time, multiomic and transcriptomic studies have redefined sCAP as a biologically heterogeneous syndrome, characterized by divergent host-response states ranging from hyperinflammation to immune dysfunction. These insights are beginning to reshape therapy, supporting phenotype-directed immunomodulation, including selective corticosteroid use and biomarker-guided interventions such as interleukin-1 blockade. In parallel, artificial intelligence and radiomics are emerging as powerful tools capable of integrating complex, multidimensional data, although their clinical utility remains largely unrealized.

Summary
sCAP should no longer be approached as a uniform infectious disease but as a spectrum of biologically distinct endotypes. The future lies in integrating pathogen detection with real-time host profiling and advanced analytics to enable truly personalized care. Without this paradigm shift, further gains in outcomes are unlikely.

Keywords
antimicrobial stewardship, host-response phenotypes, immunomodulation, molecular diagnostics, precision medicine, severe community-acquired pneumonia

INTRODUCTION

Community-acquired pneumonia (CAP) remains a major driver of infectious disease mortality worldwide, imposing a substantial burden on healthcare systems [1]. While most cases are managed outside the ICU, a vulnerable subset progresses to severe disease requiring intensive care [2]. Severe CAP (sCAP), defined by respiratory failure or septic shock, represents the most critical manifestation of this syndrome and continues to carry high mortality rates, typically 25–40%, despite advances in antimicrobial therapy and supportive care [3].

Management has traditionally been pathogen-centric, guiding empiric antibiotic therapy based on presumed causative organisms. However, this framework does not fully reflect the biological complexity of severe disease. Outcomes in sCAP are increasingly recognized to result from the interplay between pathogen characteristics, host immune response,

[a]Department of Intensive Care Medicine, Multidisciplinary Intensive Care Research Organization (MICRO), St James' Hospital, [b]School of Medicine, Trinity College Dublin, [c]Trinity Centre for Biomedical Engineering (TCBE), Dublin, Ireland, [d]Geriatric Research, Eduation and Clinical Center and South Texas Veterans Health Care System, [e]Department of Medicine, University of Texas Health San Antonio, San Antonio, TX, USA and [f]School of Medicine, Institut D'Investigacions August Pi I Sunyer (IDIBAPS) Ciberes, University of Barcelona, Barcelona, Spain

Correspondence to Professor Ignacio Martin-Loeches, Multidisciplinary Intensive Care Research Organization, St James's Hospital, James's St, Saint James, Dublin 8, D08 NHY1, Ireland.
E-mail: drmartinloeches@gmail.com

Curr Opin Crit Care 2026, 32:000–000
DOI:10.1097/MCC.0000000000001410

KEY POINTS

- sCAP remains a high-mortality syndrome despite advances in antimicrobial and supportive therapies.
- Molecular diagnostics have expanded pathogen detection but have not consistently improved antimicrobial stewardship or outcomes.
- Host-response heterogeneity, spanning hyperinflammatory and immunosuppressed states, is a key determinant of clinical trajectory.
- Future management will require integrated, phenotype-driven strategies combining pathogen identification with host-directed therapies.

and the lung microbial environment [4]. In parallel, host-response heterogeneity has emerged as a key determinant of clinical trajectory, with patients exhibiting a spectrum from hyperinflammation to immune dysfunction, influenced by age, comorbidities, and immunosenescence [5]. These insights support a shift toward a precision-based approach, integrating microbiological data with host-response profiling to enable more individualized and effective management strategies [6].

THE EVOLVING EPIDEMIOLOGY AND MICROBIAL LANDSCAPE

The microbiology of sCAP remains heterogeneous and context-dependent, influenced by geographic region, patient comorbidities, vaccination coverage, and local antimicrobial resistance patterns. *Streptococcus pneumoniae* continues to be the most frequently identified bacterial pathogen globally, followed by *Haemophilus influenzae*, *Staphylococcus aureus*, and atypical organisms such as *Legionella pneumophila*[2,7]. Despite this variability, sCAP is still generally considered a predominantly monomicrobial infection in routine clinical practice.

The increasing use of molecular diagnostic techniques has expanded the detection of respiratory pathogens, particularly viruses. Rapid molecular diagnostic testing studies have demonstrated that viral pathogens, including influenza virus, respiratory syncytial virus (RSV), severe acute respiratory syndrome coronavirus (e.g. SARS-CoV-2) and human metapneumovirus, are frequently identified in patients with severe pneumonia, either as primary pathogens or in association with bacterial infection. RSV is increasingly recognized as a relevant cause of severe disease in adults, particularly in older and comorbid populations, while parainfluenza viruses play a notable role in immunocompromised hosts [8]. However, the higher diagnostic yield associated with these technologies must be interpreted cautiously, as increased detection does not necessarily equate to causation.

Viral–bacterial interactions are clinically relevant and pathogen-specific. *S. pneumoniae* remains the most common bacterial co-pathogen in influenza-associated pneumonia, reflecting well described synergistic mechanisms between viral infection and secondary bacterial invasion [9–11]. In contrast, bacterial co-infection appears less frequent in COVID-19, particularly at presentation, although it may increase during the course of critical illness [12]. These differences highlight the importance of distinguishing between true co-infection, secondary infection, and direct microbial detection [13,14].

Recent advances in molecular microbiology, including next-generation sequencing (NGS), have further highlighted the presence of multiple microorganisms within the lower respiratory tract during episodes of pneumonia [15]. Importantly, these findings should not be interpreted as evidence that sCAP is uniformly polymicrobial. Rather, they suggest a complex ecological environment in which microbial coexistence and pathogen–pathogen interactions, together with host immune responses, shape disease expression.

RAPID MOLECULAR DIAGNOSTICS AND THE STEWARDSHIP DISCONNECT

Traditional culture-based microbiological techniques, primarily relying on sputum and blood, are limited by low sensitivity and identify a causative pathogen in only a minority of pneumonia cases. This diagnostic gap has driven increasing adoption of rapid molecular diagnostic technologies. Rapid molecular diagnostic testing panels capable of detecting a broad range of respiratory pathogens are now widely integrated into clinical practice (Table 1). These assays enable rapid identification of viral pathogens and atypical bacteria within hours of admission, with the potential to support early targeted antimicrobial therapy.

Clinical studies consistently demonstrate that rapid molecular testing substantially increases diagnostic yield. A randomized controlled trial comparing multiplex PCR combined with standard microbiology vs. conventional testing alone in hospitalized CAP patients reported a significant increase in etiological diagnosis (63.9 vs. 2%) [16▪▪]. Similarly, European data have shown that routine PCR testing accelerates targeted antimicrobial therapy [17]. In ICU settings, multiplex bacterial PCR performed on bronchoalveolar lavage samples has been associated with earlier antibiotic de-escalation [18], while multicentre data

Table 1. Precision framework for severe community-acquired pneumonia: from traditional to integrated management

Domain	Traditional approach	Emerging precision approach	Clinical implication
Microbiology	Culture-based, low yield	Multiplex PCR, mNGS	Faster pathogen detection but requires interpretation
Pathogen model	Monomicrobial	Viral + polymicrobial ecosystems	Avoid overinterpretation of co-detection
Antibiotic strategy	Broad empiric therapy	Risk-based + early de-escalation	Requires stewardship integration
Host response	Largely ignored	Phenotypes (hyperinflammation vs. immune dysfunction)	Guides immunomodulation
Immunotherapy	Empirical (corticosteroids debated)	Phenotype-guided (corticosteroids, IL-1 blockade)	Precision targeting
Diagnostics	Static, episodic	Real-time, multimodal integration	Dynamic decision-making
AI/analytics	Minimal role	Predictive + integrative models	Still early, needs validation

mNGS, metagenomic next-generation sequencing.

from France have demonstrated reduced unnecessary antibiotic use in the emergency department when viral pathogens are identified [19].

Despite these advances, the clinical impact of rapid molecular diagnostics remains inconsistent. In the randomized trial by Abelenda-Alonso *et al.* [16▪▪], improved microbiological yield and faster pathogen identification did not translate into a significant reduction in overall antibiotic exposure. This highlights a persistent gap between diagnostic capability and therapeutic decision-making.

This disconnect reflects a broader structural issue in critical care. Clinicians frequently initiate and maintain broad-spectrum antimicrobial therapy in sCAP due to the perceived risk of undertreatment and clinical deterioration. This approach is reinforced by guideline frameworks that prioritize early adequate empirical coverage, often without clear strategies for safe de-escalation. As a result, the potential of rapid diagnostics to improve antimicrobial stewardship remains limited by entrenched prescribing behaviours and a risk-averse clinical culture [20].

The fundamental limitation lies not in PCR technology itself, but in its incomplete integration into antimicrobial stewardship frameworks. While molecular diagnostics can improve antimicrobial prescribing appropriateness, moderate-certainty to high-certainty evidence indicates that they do not meaningfully reduce overall antibiotic use or improve patient outcomes, particularly in adult populations. Their impact, therefore, appears largely confined to process measures rather than hard clinical endpoints.

Without structured stewardship support, increased diagnostic sensitivity may paradoxically promote overtreatment, particularly in the context of polymicrobial detections of uncertain clinical relevance. While multiplex molecular panels improve pathogen detection compared with conventional methods, their clinical impact depends critically on how results are interpreted and acted upon [21,22▪▪].

The value of molecular diagnostics in sCAP therefore extends beyond detection alone, requiring deliberate integration into decision-making pathways capable of guiding therapy and overcoming therapeutic inertia [23].

VIRAL BURDEN AND THE LIMITS OF ANTIBIOTIC DE-ESCALATION

One of the most important insights arising from modern molecular diagnostics is the magnitude of the respiratory viral burden. The recognition that viruses account for a substantial proportion of CAP cases challenges longstanding assumptions that bacterial pathogens are the primary drivers of severe disease. Multiplex respiratory panels consistently demonstrate a significant viral contribution that was largely undetected using conventional culture-based diagnostics [24].

However, translating these findings into clinical decision-making remains challenging. Detection of viral nucleic acid does not exclude concurrent bacterial co-infection, and viral–bacterial interactions may exacerbate lung injury through dysregulated host responses. Consequently, identification of a viral pathogen alone has not reliably enabled clinicians to withhold or discontinue antibiotics, particularly in critically ill patients [25].

This limitation reflects a key unmet need: the absence of robust, standardized tools to distinguish colonization from active infection and to identify the dominant driver of disease. Until integrated diagnostic strategies, potentially combining molecular testing with host-response biomarkers can

provide this level of discrimination, clinicians will continue to default to empirical antibacterial therapy [26]. Thus, while molecular diagnostics have demonstrated that the burden of purely bacterial pneumonia has likely been overestimated, the ability to safely act on this knowledge remains limited [27].

Building on these limitations, interest has expanded toward broader, untargeted diagnostic approaches aimed at capturing the full complexity of the pulmonary microbial environment. While multiplex PCR has significantly improved pathogen detection within predefined panels, it remains inherently constrained by target selection [28]. This has led to the emergence of metagenomic NGS (mNGS) as a complementary strategy, offering a more comprehensive and unbiased assessment of the respiratory microbiome [29,30].

REFINING EMPIRIC ANTIMICROBIAL STRATEGIES

Despite the evolution of diagnostic tools, the immediate administration of empiric antimicrobial therapy remains the cornerstone of early management in sCAP. A persistent clinical challenge lies in the rapid identification of patients at high risk for infection with drug-resistant pathogens [31]. Inadequate initial antimicrobial coverage is consistently associated with increased mortality; however, the indiscriminate use of broad-spectrum agents contributes to microbiome disruption and accelerates antimicrobial resistance [32]. Established clinical risk factors for resistant pathogens include prior antibiotic exposure, recent hospitalization, significant comorbidities, structural lung disease, and residence in long-term care facilities [2].

Current international guidelines recommend combination therapy with a β-lactam antibiotic and a macrolide for patients requiring ICU admission with sCAP [2]. This regimen provides broad coverage against typical pathogens while also targeting atypical organisms, such as *Legionella* spp. Emerging high-quality evidence supports this approach. A large network meta-analysis including over 8000 patients with sCAP demonstrated that β-lactam–macrolide combination therapy was associated with lower mortality compared with alternative empiric strategies, including β-lactam monotherapy or β-lactam–fluoroquinolone combinations [33].

The benefit of macrolides (especially clarithromycin [34]) likely extends beyond their antimicrobial activity, and many authors suggest to maintain for at least 3 days despite of negative *Legionella* infection [35,36]. Macrolides exhibit immunomodulatory effects, including attenuation of pro-inflammatory cytokine production, modulation of neutrophil function, and reduction of airway inflammation. These effects may contribute to improved outcomes by mitigating dysregulated host responses and limiting lung injury in severe infection [33].

Equally important is the ongoing shift away from outdated empiric practices, particularly the routine use of antianaerobic coverage in suspected aspiration pneumonia. Earlier assumptions regarding the predominance of anaerobic pathogens were based on historical microbiological data [37]. Contemporary evidence, including molecular diagnostics, suggests that obligate anaerobes are infrequent primary pathogens in community-onset pneumonia [38]. Observational studies have not demonstrated a clear benefit of routine antianaerobic therapy, while highlighting potential harms, including microbiome disruption and an increased risk of *Clostridioides difficile* infection [39]. Current consensus therefore supports reserving antianaerobic coverage for patients with clear evidence of lung abscess, necrotizing pneumonia, or empyema [40].

HOST-RESPONSE-DRIVEN PRECISION MEDICINE AND TARGETED IMMUNOMODULATION IN SEVERE COMMUNITY-ACQUIRED PNEUMONIA

Perhaps the most profound conceptual shift in modern critical care is the recognition that the host response, rather than the identity of the pathogen alone, is the dominant determinant of outcome in sCAP. Precision medicine in this setting will not be achieved by simply identifying more pathogens, but by understanding how and why the host response becomes maladaptive [41]. sCAP is now increasingly understood as a biologically heterogeneous syndrome [42]. Data from recent transcriptomic and multiomic studies in CAP, including severe disease, indicate that the host response is highly heterogeneous and characterized by distinct immune activation states rather than a uniform inflammatory process. These studies consistently identify patterns ranging from hyperinflammatory responses driven by innate immune activation and cytokine signalling to states of immune dysfunction marked by features of cellular exhaustion, impaired adaptive immunity, and susceptibility to secondary infections. Importantly, these host-response signatures are closely associated with disease severity and clinical trajectories, highlighting the central role of host biology in determining outcomes beyond pathogen identification alone [43,44]. The integration of real-time host-response biomarkers, multiomic profiling, and clinical data to enable bedside phenotyping represents one of the most promising avenues for improving outcomes in sCAP, as recently highlighted in a prospective multicohort study [45].

This paradigm shift has direct implications for immunomodulatory strategies. The long-standing debate surrounding corticosteroid use has now largely evolved: contemporary evidence supports their use in sCAP with some considerations. Patients with the worst presentation (shock), often identified by elevated c-reactive protein (CRP) and systemic inflammatory markers [46▪▪], are more likely to benefit [47], however, with some remaining questions to identify the right patient without expanding the treatment to everyone admitted to the hospital with CAP [48]. In contrast, indiscriminate use in patients with viral pneumonia or those already immunosuppressed may be harmful, increasing the risk of uncontrolled viral replication and secondary infections [49,50].

Emerging evidence further supports a move toward targeted immunomodulation beyond corticosteroids. Studies evaluating interleukin-1 blockade, particularly with anakinra, have demonstrated that biomarker-guided approaches can identify subgroups of patients with dysregulated inflammation who may derive significant benefit [51]. The work led by Giamarellos-Bourboulis and colleagues in CAP highlights the feasibility of using host-response markers to guide immunotherapy, moving toward a precision-based model rather than empirical treatment [52▪▪]. Similarly, ongoing exploration of other immunomodulatory pathways, including IL-6 inhibition, Granulocyte-macrophage colony-stimulating factor (GM-CSF) modulation, and immune checkpoint restoration reflects a broader shift toward tailoring therapy based on immune status rather than disease label [53,54].

Ultimately, the future of sCAP management lies in the convergence of microbiological diagnostics and host-response profiling. Rather than viewing infection solely through the lens of pathogen identification, a dual-axis model integrating pathogen and host biology will be required (Fig. 1). Only through this approach can immunomodulatory therapies be deployed safely and effectively, transforming sCAP from a syndromic entity into a set of biologically defined, treatable endotypes [55▪▪].

ARTIFICIAL INTELLIGENCE AND RADIOMICS: PROMISE VS. REALITY

As the volume of patient data explodes, artificial intelligence, machine learning, and large language models are increasingly positioned as transformative decision-support tools [56]. A highly promising frontier is the application of advanced imaging analytics to standard diagnostic radiology. Recent advances in imaging analytics have highlighted the potential of radiomics and artificial intelligence to improve risk stratification in pneumonia. Computed tomography (CT), particularly when performed early in the diagnostic pathway, provides detailed assessment of the extent and distribution of pulmonary involvement in suspected CAP, with imaging burden contributing to diagnostic refinement and influencing clinical management decisions [57]. In a recent study developing a CT-based radiomics model for CAP, quantitative imaging features demonstrated robust performance for identifying severe disease and supporting early risk stratification, highlighting their potential as noninvasive biomarkers to guide clinical decision-making [55▪▪].

Beyond imaging, machine learning algorithms are actively being trained to ingest a chaotic mix of clinical variables, laboratory results, and genomic data to predict disease severity and dynamically guide antibiotic therapy. However, experts caution that this field remains in its infancy, an early translational phase. The vast majority of these artificial intelligence models are trained on retrospective datasets, suffer from a critical lack of external validation, and are fundamentally isolated from actual clinical workflows [5,30,58]. Furthermore, the true incremental benefit of these tools compared with the judgment of an experienced intensivist remains unproven. The ultimate potential of artificial intelligence will not be realized through simplistic mortality prediction, but through its unique ability to fuse highly fragmented, multidimensional data, microbiology, host phenotyping, and advanced imaging, into immediate, coherent, and actionable clinical decisions at the bedside.

CONCLUSION

The management of sCAP is undergoing a fundamental shift toward precision medicine. Advances in molecular diagnostics, host-response profiling, imaging analytics, and artificial intelligence are redefining pneumonia as a biologically heterogeneous syndrome rather than a uniform infectious entity. This evolving perspective challenges traditional approaches based solely on pathogen identification and static severity scores.

Future care will rely on integrated, real-time frameworks that combine microbiological data, immune signatures, physiological trends, and imaging-derived features to guide decision-making at the bedside. These systems have the potential not only to improve risk stratification, but to actively support therapeutic choices, enabling more rational antimicrobial use, targeted immunomodulation, and earlier recognition of treatment failure.

A key priority will be the development of clinically usable platforms that translate complex data into actionable insights. This includes adaptive decision-support

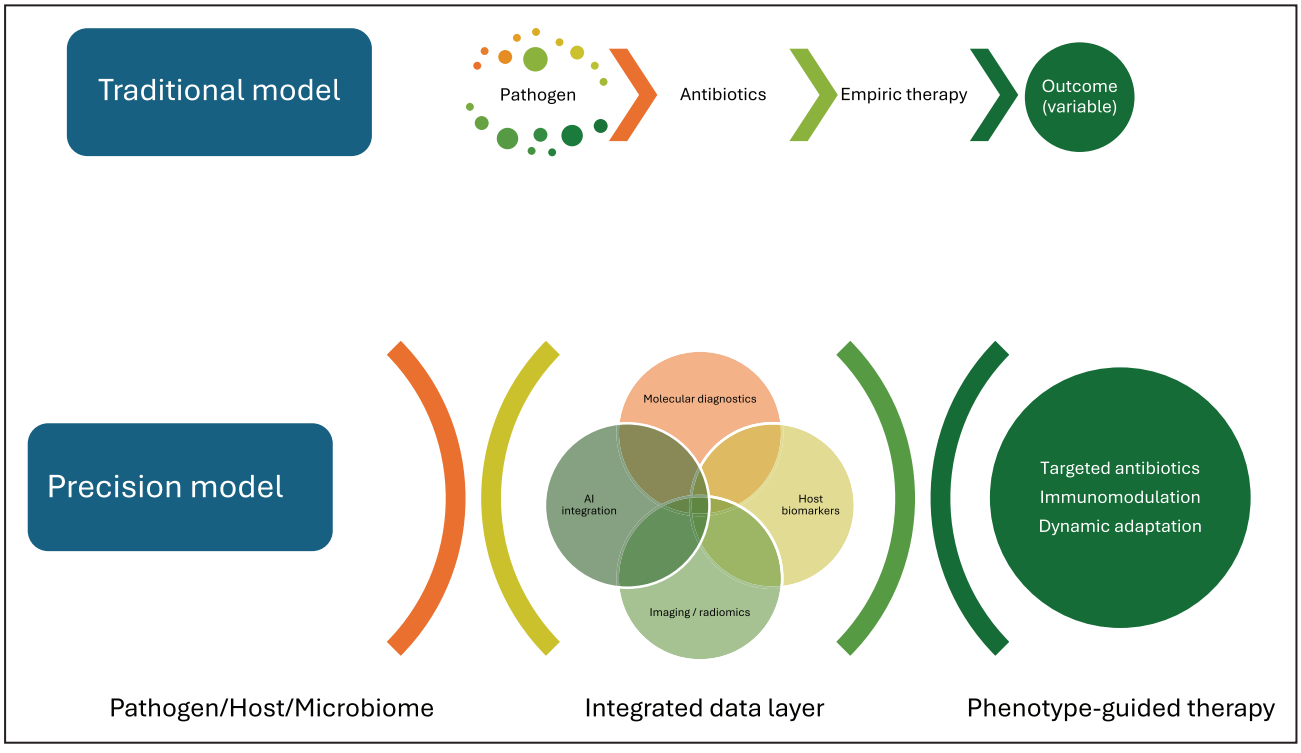


FIGURE 1. From pathogen-centric to precision severe community-acquired pneumonia model.

tools, trajectory-based monitoring, and predictive models that evolve with the patient's condition. Importantly, the integration of host-response phenotyping into routine care offers a pathway to move beyond empirical treatment and toward mechanism-based therapy.

Equally, future clinical trials must reflect this paradigm shift. Enrichment strategies based on biological phenotypes, rather than broad syndromic definitions, will be essential to identify treatment effects that have been obscured in previous studies. This will be particularly relevant for immunomodulatory therapies, where efficacy is likely confined to specific patient subgroups.

Ultimately, the goal is to redefine sCAP as a spectrum of distinct, treatable endotypes. Achieving this will require alignment between clinical practice, translational research, and data science, alongside tools that are both robust and practical for frontline use. If successfully implemented, this approach offers a realistic opportunity to improve outcomes and reduce the persistently high mortality associated with this condition.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Feldman C, Anderson R. Community-acquired pneumonia: pathogenesis of acute cardiac events and potential adjunctive therapies. Chest 2015; 148: 523–532.
2. Martin-Loeches I, Torres A, Nagavci B, *et al.* ERS/ESICM/ESCMID/ALAT guidelines for the management of severe community-acquired pneumonia. Intensive Care Med 2023; 49:615–632.
3. Asis A, McMahon D, Fujitani S, *et al.* Severe community-acquired pneumonia: an integral approach. J Intensive Care 2026; 14:21.
4. Dequin PF, Torres A, Bassetti M, *et al.* Severe community-acquired pneumonia: current concepts and controversies. Intensive Care Med 2026; 52:118–130.
5. Martin-Loeches I, Reyes LF, Rodriguez A. Severe community-acquired pneumonia (sCAP): advances in management and future directions. Thorax 2025; 80:565–575.
6. Chigozie VU, Enyi EO, Akwari AA, Esimone CO. Host-microbe interactions at barrier tissues and immunomodulation: a scoping review. Discov Bacteria 2025; 2:26.
7. Pickens CI, Gao CA, Morales-Nebreda L, Wunderink RG. Microbiology of severe community-acquired pneumonia and the role of rapid molecular techniques. Semin Respir Crit Care Med 2024; 45:158–168.
8. Nguyen-Van-Tam JS, O'Leary M, Martin ET, *et al.* Burden of respiratory syncytial virus infection in older and high-risk adults: a systematic review and meta-analysis of the evidence from developed countries. Eur Respir Rev 2022; 31:220105.
9. McCullers JA. The co-pathogenesis of influenza viruses with bacteria in the lung. Nat Rev Microbiol 2014; 12:252–262.
10. Martin-Loeches I, M. JS, Vincent JL, *et al.* Increased incidence of co-infection in critically ill patients with influenza. Intensive Care Med 2017; 43:48–58.

11. Arranz-Herrero J, Presa J, Rius-Rocabert S, *et al.* Determinants of poor clinical outcome in patients with influenza pneumonia: a systematic review and meta-analysis. Int J Infect Dis 2023; 131:173–179.

12. Rodríguez A, Gómez J, Martín-Loeches I, *et al.* A machine learning approach to determine risk factors for respiratory bacterial/fungal coinfection in critically ill patients with influenza and SARS CoV-2 infection: a Spanish perspective. Antibiotics (Basel) 2024; 13:968.

13. Musher DM. Bacterial coinfection in COVID-19 and influenza pneumonia. Am J Respir Crit Care Med 2021; 204:498–500.

14. Rouzé A, Martin-Loeches I, Povoa P, *et al.* coVAPid Study Group. Early bacterial identification among intubated patients with COVID-19 or influenza pneumonia: a European Multicenter Comparative Clinical Trial. Am J Respir Crit Care Med 2021; 204:546–556.

15. Martin-Loeches I, Pereira JG, Teoh TK, *et al.* Molecular antimicrobial susceptibility testing in sepsis. Future Microbiol 2024; 19:61–72.

16. ■■ Abelenda-Alonso G, Calatayud L, Rombauts A, *et al.* Multiplex real-time PCR in noninvasive respiratory samples to reduce antibiotic use in community-acquired pneumonia: a randomised trial. Nat Commun 2024; 15:7098.

Demonstrates that improved molecular pathogen detection in CAP does not automatically translate into reduced antibiotic exposure, highlighting the stewardship gap.

17. Markussen DL, Serigstad S, Ritz C, *et al.* Diagnostic stewardship in community-acquired pneumonia with syndromic molecular testing: a randomized clinical trial. JAMA Netw Open 2024; 7:e240830.

18. Darie AM, Khanna N, Jahn K, *et al.* Fast multiplex bacterial PCR of bronchoalveolar lavage for antibiotic stewardship in hospitalised patients with pneumonia at risk of Gram-negative bacterial infection (Flagship II): a multicentre, randomised controlled trial. Lancet Respir Med 2022; 10:877–887.

19. Cantais A, Pillet S, Rigaill J, *et al.* OPTIPAC study group. Impact of respiratory pathogens detection by a rapid multiplex polymerase chain reaction assay on the management of community-acquired pneumonia for children at the paediatric emergency department. A randomized controlled trial, the Optimization of Pneumonia Acute Care (OPTIPAC) study. Clin Microbiol Infect 2025; 31: 64–70.

20. Wanat M, Hoste ME, Anastasaki M, *et al.* Clinician and patient experiences with point-of-care testing for acute respiratory infections in primary care: a qualitative process evaluation of the PRUDENCE trial. Lancet Primary Care 2026; 2:

21. Giménez E, Clari M, Albert E, *et al.* Performance of the BIOFIRE® Filmarray Pneumonia Plus Panel for quantifiable bacterial targets compared to semi-quantitative culture methods: a systematic review and meta-analysis. J Infect 2026; 92:106683.

22. ■■ Li Q, Zhou Q, Fan J, *et al.* Impact of molecular point-of-care testing for respiratory pathogens on antibiotic use and clinical outcomes in acute respiratory tract infections: a systematic review and meta-analysis. EClinicalMedicine 2026; 92:103799.

Important meta-analysis showing that molecular POCT improves prescribing appropriateness but has limited effect on overall antibiotic use or hard outcomes.

23. de Albuquerque Pessoa Dos Santos Y, Tomazini BM, Dos Santos MHC, *et al.* Impact of syndromic molecular diagnostics on antimicrobial adequacy and time to therapy in critically ill patients with pneumonia: a systematic review and meta-analysis of randomized trials. Crit Care 2025; 29:379.

24. Nickbakhsh S, Thorburn F, VON Wissmann B, *et al.* Extensive multiplex PCR diagnostics reveal new insights into the epidemiology of viral respiratory infections. Epidemiol Infect 2016; 144:2064–2076.

25. Martin-Loeches I, van Someren Gréve F, Schultz MJ. Bacterial pneumonia as an influenza complication. Curr Opin Infect Dis 2017; 30:201–207.

26. Martin-Loeches I. When colonisation becomes confusion: a cautionary note on pneumonia aetiology. Eur Respir J 2025; 66:2501205.

27. Carlton HC, Savović J, Dawson S, *et al.* Novel point-of-care biomarker combination tests to differentiate acute bacterial from viral respiratory tract infections to guide antibiotic prescribing: a systematic review. Clin Microbiol Infect 2021; 27:1096–1108.

28. Rodríguez-Gómez M, Martínez-Sagasti F, Calle-Romero M, *et al.* RAPID-CARE: rapid antibiotic optimization in the ICU after implementation of a pneumonia multiplex PCR test-a real-world evaluation. Antibiotics (Basel) 2025; 14:1084.

29. Bustos IG, Martinez-Lemus LF, Reyes LF, Martin-Loeches I. Transforming microbiological diagnostics in nosocomial lower respiratory tract infections: innovations shaping the future. Diagnostics (Basel) 2025; 15:265.

30. O'Reilly D, McGrath J, Martin-Loeches I. Optimizing artificial intelligence in sepsis management: opportunities in the present and looking closely to the future. J Intensive Med 2024; 4:34–45.

31. Reyes LF, Conway Morris A, Serrano-Mayorga C, *et al.* Community-acquired pneumonia. Lancet 2025; 406:2371–2388.

32. Patra M, Gupta AK, Kumar D, Kumar B. Antimicrobial resistance: a rising global threat to public health. Infect Drug Resist 2025; 18:5419–5437.

33. Wang M, Zhang J, Wang X, *et al.* Comparison of initial empirical antibiotic regimens in severe community-acquired pneumonia: a network meta-analysis. BMC Pulm Med 2025; 25:246.

34. Kyriazopoulou E, Sinapidis D, Halvatzis S, *et al.* Survival benefit associated with clarithromycin in severe community-acquired pneumonia: a matched comparator study. Int J Antimicrob Agents 2020; 55:105836.

35. Garin N, Genné D, Carballo S, *et al.* β-Lactam monotherapy vs β-lactam-macrolide combination treatment in moderately severe community-acquired pneumonia: a randomized noninferiority trial. JAMA Intern Med 2014; 174: 1894–1901.

36. Restrepo MI, Mortensen EM, Waterer GW, *et al.* Impact of macrolide therapy on mortality for patients with severe sepsis due to pneumonia. Eur Respir J 2009; 33:153–159.

37. Chanderraj R, Baker JM, Kay SG, *et al.* In critically ill patients, antianaerobic antibiotics increase risk of adverse clinical outcomes. Eur Respir J 2023; 61: 2200910..

38. Marin-Corral J, Pascual-Guardia S, Amati F, *et al.* GLIMP investigators. Aspiration risk factors, microbiology, and empiric antibiotics for patients hospitalized with community-acquired pneumonia. Chest 2021; 159:58–72.

39. Yoshimatsu Y, Aga M, Komiya K, *et al.* The clinical significance of anaerobic coverage in the antibiotic treatment of aspiration pneumonia: a systematic review and meta-analysis. J Clin Med 2023; 12:1992.

40. Bai AD, Srivastava S, Digby GC, *et al.* Anaerobic antibiotic coverage in aspiration pneumonia and the associated benefits and harms: a retrospective cohort study. Chest 2024; 166:39–48.

41. Moore AR, Zheng H, Ganesan A, *et al.* A consensus immune dysregulation framework for sepsis and critical illnesses. Nat Med 2025; 31:4084–4096.

42. Antcliffe DB, Burrell A, Boyle AJ, *et al.* Sepsis subphenotypes, theragnostics and personalized sepsis care. Intensive Care Med 2025; 51:756–768.

43. Hong L, Suo L, Chang K, *et al.* Longitudinal profiling of host response and oropharyngeal respiratory microbiome reveals dynamic alterations during recovery from community-acquired pneumonia. Biosaf Health 2025; 7: 152–165.

44. Song W, Yang Q, Lv H, *et al.* Prospective multicenter study identifying prognostic biomarkers and microbial profiles in severe CAP using BALF, blood mNGS, and PBMC transcriptomics. Sci Rep 2025; 15:16252.

45. Xiao K, Cao Y, Yan P, *et al.* A large-scale single-cell atlas reveals the peripheral immune panorama of bacterial pneumonia. Am J Respir Crit Care Med 2025; 211:2363–2381.

46. ■■ Smit JM, Van Der Zee PA, Stoof SCM, *et al.* Predicting benefit from adjuvant therapy with corticosteroids in community-acquired pneumonia: a data-driven analysis of randomised trials. Lancet Respir Med 2025; 13:221–233.

A key article supporting phenotype-informed corticosteroid use by identifying subgroups most likely to benefit.

47. Martin-Loeches I, Nagavci B, Torres A. Final approval for corticosteroids in severe CAP? For sure, in septic shock. Crit Care 2023; 27:342.

48. Reyes LF, Martin-Loeches I. Corticosteroids in community-acquired pneumonia: a step forward, but questions remain. Lancet Respir Med 2025; 13: 191–193.

49. Gordon M, Ramirez P. The role of corticosteroids in severe viral pneumonia: lessons from COVID-19 and influenza. Pneumonia (Nathan) 2026; 18:6.

50. Tian X, Wei D, Meng S, *et al.* Impact of glucocorticoid therapy on short- and long-term mortality in immunocompromised patients with community-acquired pneumonia in the ICU: a retrospective cohort study. BMC Infect Dis 2026; 26: 417.

51. Shakoory B, Carcillo JA, Chatham WW, *et al.* Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: reanalysis of a prior phase III trial. Crit Care Med 2016; 44:275–281.

52. ■■ Tavoulareas G, Kontakou-Zoniou O, Antonakos N, *et al.* Efficacy of anakinra in reducing progression to organ dysfunction in patients with pneumonia (INSPIRE): a randomised, double-blind, placebo-controlled, phase IIa trial. Lancet Reg Health Eur 2026; 62:101573.

Provides prospective evidence that biomarker-guided immunomodulation may be feasible in pneumonia.

53. Gou X, Xu W, Liu Y, *et al.* IL-6 prevents lung macrophage death and lung inflammation injury by inhibiting GSDME- and GSDMD-mediated pyroptosis during pneumococcal pneumosepsis. Microbiol Spectr 2022; 10:e0204921.

54. Tavares LP, Galvao I, Ferrero MR. Novel immunomodulatory therapies for respiratory pathologies. Comprehensive Pharmacol 2022:554–594.

55. ■■ Torres A, Cilloniz C, Martin-Loeches I. Phenotype-based stratification and corticosteroid response in hyperinflammatory severe community-acquired pneumonia. Intensive Care Med 2026; 52:813–816.

Reinforces the move away from one-size-fits-all therapy toward biologically defined treatment strategies in sCAP.

56. Arnold A, McLellan S, Stokes JM. How AI can help us beat AMR. NPJ Antimicrob Resist 2025; 3:18.

57. Claessens YE, Debray MP, Tubach F, *et al.* Early chest computed tomography scan to assist diagnosis and guide treatment decision for suspected community-acquired pneumonia. Am J Respir Crit Care Med 2015; 192:974–982.

58. Carbajo RS, Palma J, Martin-Loeches I. The next frontier in sepsis: connected ICU data for real-world clinical decision making. Intensive Care Med 2026; 52: 301–308.