

Advances in the causes and management of community acquired pneumonia in adults

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ABSTRACT

Community acquired pneumonia remains a common cause of morbidity and mortality. Usually, the causal organism is not identified and treatment remains empiric. Recent computed tomography and magnetic resonance imaging studies have challenged the accuracy of the clinical diagnosis of pneumonia, and epidemiologic studies are changing our perspective of what causes community acquired pneumonia, especially the role of viral pathogens and the frequent finding of multiple pathogens. The past decade has seen increasing overuse of empiric coverage of meticillin resistant *Staphylococcus aureus* and antibiotic resistant Gram negative pathogens owing to inappropriate application of guidelines for healthcare associated pneumonia. Optimal treatment remains a matter for debate, especially in very sick patients, including the role of combination antibiotic therapy and corticosteroids. Pneumonia care bundles are being defined to improve outcomes. Increased recognition of both acute and long term cardiac complications is shifting our concept of pneumonia from an acute lung disease to a multisystem problem with adverse chronic health consequences.

Introduction

Community acquired pneumonia (CAP) remains a major health concern worldwide with substantial morbidity and mortality.¹⁻³ The entire range of physicians, from primary care to intensivists and from generalists to subspecialists, will encounter CAP in one form or another.⁴ CAP is in the differential diagnosis of the respiratory tract symptoms that are the most common cause of urgent outpatient primary care and emergency department visits.^{5 6} CAP is one of the most common medical causes of admission in most healthcare systems; in the US, it is exceeded only by live births.⁷

Treatment for infections is generally based on an accurate determination of the cause. As microbiologic tests have yet to deliver on rapid, accurate pathogen based diagnosis in most patients, treatment remains empiric and is based on the likely pathogens and clinical scenario. Therefore, newer information on causes, even if determined by diagnostic tests not available in usual practice, can have implications for treatment decisions.

Pneumonia that occurs in patients known to be immunocompromised is not generally considered to be CAP because of the expanded spectrum of pathogens. Despite this, many immunocompromised patients have infections with the same causes as hosts with normal immune systems.^{8 9} Also, the range of immunosuppressants used for non-malignant disease is increasing rapidly, and many

of these patients are disproportionately prone to usual CAP pathogens.¹⁰ For this review, we will exclude the most severely immunocompromised patients—those with acute leukemias and lymphomas, recent bone marrow or solid organ transplant recipients, those receiving active chemotherapy especially with neutropenia, and those with untreated or poorly treated AIDS or known severe congenital immunodeficiency syndromes. Equally, patients presenting from the community but who have had a recent hospital admission are not treated as having CAP, as they have a spectrum of pathogens more similar to hospital acquired pneumonia.^{11 12} Finally, pneumonia that occurs in children also has very different clinical features, and studies and guidelines in adults do not necessarily apply.^{13 14} This review will therefore not discuss the management of CAP in children.

Cursory review of current guidelines for treating CAP compared with those from 20 years ago might suggest very little change in the field. In reality, a large shift in the evidence base around optimal treatment of CAP is changing how the diagnosis is made, what pathogens cause disease, and what the optimal bundle of therapies contains. This review will focus in particular on new developments in the field of CAP.

In summary, this review will focus on management of CAP in patients in hospital. The information will be appropriate for primary care practitioners and emergency

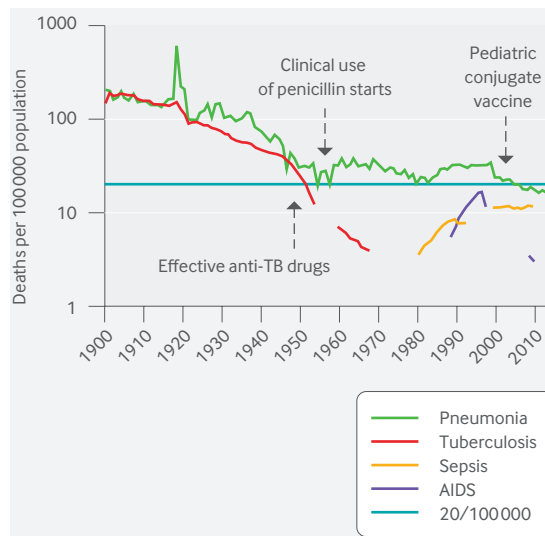


Fig 1 | Temporal trends in US mortality from pneumonia and influenza compared with other important infections since 1900 (source: Centers for Disease Control and Prevention). TB=tuberculosis

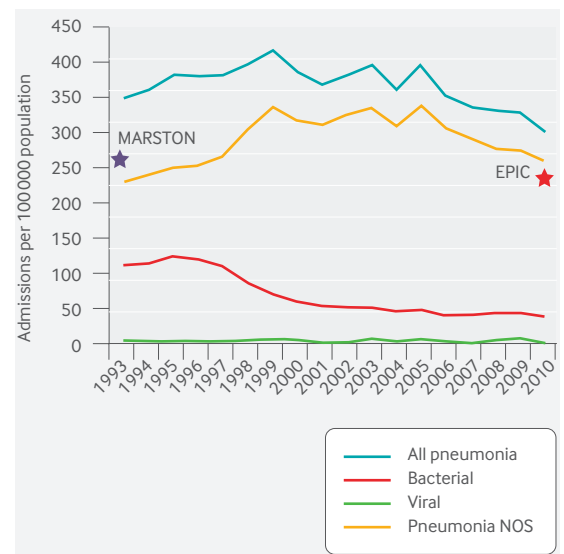


Fig 2 | Trends in discharges coded for pneumonia from the National Inpatient Sample.²⁰ NOS=not otherwise specified. Stars show two Centers for Disease Control sponsored, population based estimates^{19,21}

department physicians who would initially see these patients and start treatment. Subsequent management by hospitalists, internists, and specialists, such as infectious diseases, pulmonary, and critical care physicians, will also be covered.

Incidence

CAP is the leading infectious cause and eighth most common overall cause of death in the US.¹⁵ Pneumonia causes an even higher proportion of deaths worldwide, with 3.2 million estimated deaths globally, exceeding all other infections including tuberculosis, HIV infection, and malaria.¹ Lower respiratory tract infections are the most common cause of death in low income countries, whereas pneumonia is the only infection in the top 10 causes of death in high income economies.

Importantly, although some progress in decreasing overall mortality has been made both nationally and worldwide, the fall in deaths from pneumonia is substantially less than has been achieved recently for other infections such as diarrhea, HIV, and malaria.¹ In addition, pneumonia is often the direct cause of death ascribed to other common causes, such as Alzheimer's disease, lung cancer, and chronic obstructive lung disease.¹⁶⁻¹⁸

Figure 1 illustrates the difficulty in improving mortality due to CAP. Pneumonia and influenza have remained in the top 10 causes of death in the US since 1900. After substantial improvements in the mortality rate as a result of better hygiene and public health throughout the first part of the 20th century (note the log scale on the y axis of figure 1), once penicillin became routinely available the mortality rate from pneumonia and influenza essentially plateaued. Only in the past 10 years has the US mortality rate consistently stayed below 20 deaths per 100 000 population. Two factors likely explain this improvement in mortality—routine vaccination of children with the protein conjugate pneumococcal vaccine and public reporting of CAP process of care, mortality, and readmission rates.

The annual incidence of CAP in the US has recently been estimated at 248 cases per 10 000 adults,¹⁹ with some variation on a year-by-year basis (fig 2). The rate estimated by Jain et al in 2010-11 is very similar to that found in the previous Centers for Disease Control and Prevention (CDC) sponsored epidemiologic study from 1991.^{19,21} It also correlates fairly well with data on discharge diagnoses from the National Inpatient Sample.²⁰ In contrast, rates in other countries with different health-care systems are very different; for example, 8.1 hospital admissions per 10 000 adults in Vietnam and 31.2 per 10 000 adults in the UK.^{22,23} However, admissions for CAP have been increasing over the past 16 years in areas of England.²⁴ Different rates may partially reflect differences in age as well as healthcare settings. The incidence is clearly higher in older adults. Recent published estimates from other countries include 130.5 per 10 000 adults aged over 65 years in Malaysia,²⁵ 172.4 cases per 10 000 for adults aged 85 and over in the Netherlands,²⁶ and 29.6 per 10 000 for all ages and 76.5 for adults aged 65 and over in Germany.²⁷

Sources and selection criteria

We searched PubMed from 1 January 2007 to 1 January 2017. We chose this time span as roughly the interval since the last extensive review for the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) consensus guidelines on community acquired pneumonia was completed.¹¹ We primarily focused on original articles on “community-acquired pneumonia” listed as “clinical trials” in “humans”, “19+/adults”, and published in English. This strategy yielded 160 articles. Review of the abstracts of these manuscripts resulted in 25 being chosen for further review. Most of the manuscripts not chosen were subgroup analyses of primary studies, small single center studies with limited new information, or negative trials of agents not currently available clinically. Additional modifiers and cross search

terms including “healthcare associated pneumonia”, “community-onset pneumonia”, “viral pneumonia”, “influenza”, “*Staphylococcus aureus*”, “*Streptococcus pneumoniae*”, “mycoplasma”, and “atypical pneumonia” did not result in significant additional manuscripts. However, for specific sections, we crossed these primary search phrases with specific terms such as “corticosteroids”, “microbiome”, “microbiota”, “deep sequencing”, and “next generation sequencing” for further insights. Only articles published in English were reviewed. The final reference list is based on relevance to the topics covered in the review.

How imaging technology is challenging the clinical diagnosis of pneumonia

CAP has always been a clinical diagnosis combining features of an acute respiratory infection and a new (and consistent) infiltrate on chest radiograph. Although this is seemingly straightforward, the not infrequent disagreement between independent observers regarding presence or absence of pneumonia on re-evaluation of chest radiographs is well known.²⁸⁻³² This misdiagnosis rate is perhaps not very surprising given that various common co-pathologies, especially cardiac failure and chronic obstructive pulmonary disease, can also cause infiltrates that may be mistaken for areas of consolidation in patients with acute shortness of breath.

Until recently, no realistic alternative to plain chest radiography existed. Therefore, despite the limitations, diagnosis by the physician (including interpretation of the chest radiograph) was the gold standard for clinical studies of CAP. Two recent studies challenge the validity of this approach and the future of chest radiography in the diagnosis of CAP.

A prospective observational study in 319 patients presenting to hospital with acute respiratory symptoms consistent with CAP assessed the potential effect of chest computed tomography (CT).³³ Clinicians were asked to determine whether the patient had CAP on the basis of the clinical features (history and examination) and their interpretation of the chest radiograph; all patients then had a chest CT scan. Significant discordance between the clinician’s diagnosis and the CT determination of pneumonia occurred in nearly 40%. Most importantly, nearly a third of patients diagnosed as having pneumonia did not have any infiltrate visible on the CT scan. These findings are consistent with an observational study in emergency departments where 3423 patients had both chest radiography and a CT scan as part of routine care.³⁴ Using the CT scan as the gold standard, the sensitivity and specificity of the detection of an opacity by chest radiography were only 43.5% and 93.0% respectively.

In a smaller prospective study in 77 outpatients with CAP, findings on chest radiography were compared with those of CT scans and magnetic resonance imaging (MRI) taken at the time of diagnosis and 30 days later in all patients with positive results.³⁵ Pneumonia was identified in 32 patients by CT scan, 30 by MRI, and 23 by chest radiography. The false positive chest radiography rate was much smaller in this study with only four false positives (and none with MRI); however, all were reported

by a radiologist rather than interpreted by the clinician, and the 30 day follow-up studies were available for comparison.

Although the fact that pneumonia may be missed by chest radiography has been known for some time, overdiagnosis of pneumonia by clinicians in these studies raises the fundamental question of how many patients without pneumonia were enrolled into the clinical trials on which treatment, quality of care, and remuneration benchmarks are based. If much of what is called pneumonia is not pneumonia, potential light is also shed on discrepancies between findings of CAP studies.

A CT scan for the routine diagnostic investigation of a patient with CAP is not practical in many settings. However, the increasing availability of CT scanners in emergency departments and the ability of a modern generation of CT scanners to image as fast as and with equivalent radiation to convention chest radiography suggests this may be the future of care.^{36,37} The alternative is point-of-care ultrasonography, which can also confirm the presence of infiltrates and distinguish between parenchymal and pleural abnormalities.³⁸

Further research on the radiographic evidence for pneumonia is clearly needed. In addition to comparison of CT and ultrasonography confirmation of radiographic diagnosis, determination of whether chest radiograph negative, CT or ultrasound positive cases have the same or different pathogens, outcomes, and therefore treatment recommendations as confirmed chest radiograph positive disease is needed. In addition, the traditional approach of independent review of the actual chest radiographs by two or more clinicians is probably no longer adequate confirmation of radiographic criteria for CAP in clinical trials.

How understanding of the pathogens causing CAP is evolving

Standard pathogens

The standard list of pathogens causing CAP in any textbook starts with *Streptococcus pneumoniae* and then in varying order lists *Haemophilus influenzae*, *Staphylococcus aureus*, *Mycoplasma pneumoniae*, group A streptococci, *Legionella* species, *Chlamydia*, and *Moraxella catarrhalis*. Viral causes are usually listed somewhere in the top half a dozen pathogens, with a long list including influenza A and B, respiratory syncytial virus, adenovirus, and a variety of coronaviruses.

Data on the causes of CAP predominantly come from studies using conventional culture techniques, with or without serologic tests, all of which have substantial limitations. Considerable improvements in the sensitivity, availability, and affordability of molecular pathogen testing in the past decade now influence our understanding of the causes of CAP. At the same time, the conjugate pneumococcal vaccines have affected pneumococcal disease in adults,³⁹ even when given only to children.⁴⁰ This decline in pneumococcal disease has been accompanied by a decline in total hospital admissions for pneumonia, at least in the US.⁴¹

A 2015 study of CAP in the US by the CDC found that *S pneumoniae* was only the third most common cause detected, after rhinovirus and influenza (fig 3).¹⁹ A

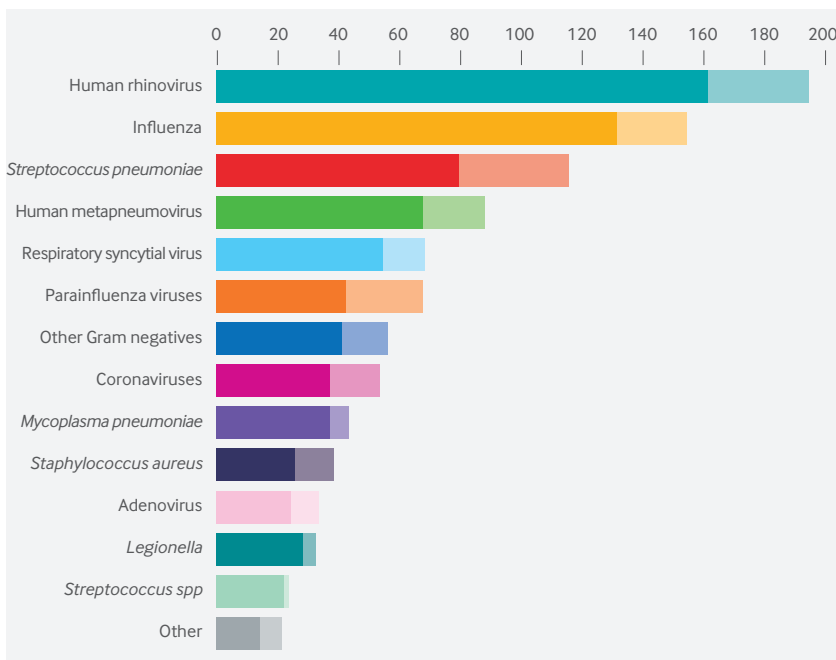


Fig 3 | Pathogens detected in patients with radiographic community acquired pneumonia from the Centers for Disease Control EPIC study. Lighter bars indicate co-detections of more than one pathogen. From Jain et al¹⁹

Norwegian study that also used a wide array of diagnostic techniques found that *S pneumoniae* remained the most common cause identified, but the proportion due to other pathogens, especially viruses, was much higher than traditionally reported.⁴² The most important observation in both of these recent studies was that two or more pathogens were identified in more than one third of cases, typically a virus/bacteria combination.^{19,42}

A key unresolved question is whether the detection of a virus in the upper airways reflects the pneumonia pathogen(s), particularly in the setting of multiple detections. Some viruses persist for weeks after acute infection, raising the question of whether the viruses detected were the residual of a resolving, initial upper respiratory tract infection that set the scene for secondary bacterial pneumonia. Data suggest that higher counts of virus in the upper airways is more likely to correlate with viral pneumonia, at least in children,⁴³ and future studies using serial quantitative assays may help to answer this important clinical question.

Newer pathogens

New pathogens continue to emerge as causes of CAP. Metapneumovirus, first reported in 2001,⁴⁴ is now often identified as one of the top half dozen pathogens causing CAP. Although it is typically associated with milder disease, fatal cases of metapneumovirus pneumonia have been reported. Coronaviruses have also emerged as major epidemic threats, first with severe acute respiratory syndrome and more recently with Middle East respiratory syndrome. Influenza also continues to be a threat, with concerns about the potential for several strains of avian influenza, particularly H5N1 and H7N9, to mutate enough to allow sustained human-to-human transmission with resultant pandemics.

Antibiotic resistance

Penicillin resistance in *S pneumoniae* has been a concern. However, apart from occasional case reports, little evidence exists to justify modification of guideline concordant empiric antibiotic regimens in any region. Macrolide resistance in pneumococci and *Mycoplasma* is greater than β lactam resistance in most areas, but the clinical importance remains unclear. In pneumococci, macrolide resistance seems to have little effect on the outcome of patients admitted to hospital,⁴⁵ in part because macrolide monotherapy is not recommended in this setting. Macrolide resistance in *M pneumoniae* is reported to be associated with prolonged symptoms and slower resolution of fever.⁴⁶ Therefore, in confirmed *M pneumoniae* infections with a slow clinical response, switching to an alternate agent such as a tetracycline or fluoroquinolone would be appropriate.

Meticillin resistant *S aureus*

The rise of meticillin resistant *S aureus* (MRSA) has predominantly been a feature of hospital acquired infections. However, true community acquired MRSA infections have recently been detected and are becoming increasingly common, especially in the US. Many MRSA strains, as well as related meticillin sensitive strains, secrete specific exotoxins that can lead to severe necrotizing pneumonia,⁴⁷ although the exotoxin repertoire may vary geographically. To date, community acquired MRSA has not been sufficiently widespread to require empiric coverage,^{48,49} but clinicians need to know their local epidemiology, especially in very sick (that is, intensive care) patients. The USA300 clone that causes the most dramatic and lethal CAPs in North America has a fairly characteristic clinical presentation (box 1).^{50,51} Suspicion of this pathogen warrants adjunctive or definitive treatment with antibiotics that suppress toxin production, such as linezolid or clindamycin, even for meticillin susceptible strains.^{52,53} Cultures are always positive, but the emergence of rapid molecular diagnostic tests allows even earlier discontinuation of anti-MRSA treatment.^{54,55}

The lung microbiome

Discovery of a normal lung microbiome that includes many of the bacteria commonly causing CAP, such as *S pneumoniae* and *Mycoplasma* spp, threatens the primary concept of pneumonia pathogenesis.^{56,57} Aspiration or inhalation of “pathogenic” bacteria into sterile alveoli is thought to be the primary step in development of pneumonia. Rather than occurring in a sterile environment, CAP may result from a dysbiosis of the normal flora,⁵⁸

Box 1 | Clinical features suggestive of community acquired MRSA

- Rapid progression of pulmonary infiltrates or pleural effusions
- Evidence of lung necrosis at presentation or early in course
- “Dirty dishwasher” appearance of pleural fluid
- Gross hemoptysis
- Young previously healthy patient
- History of MRSA skin lesions
- Erythematous rash—toxic shock, scalded skin syndromes

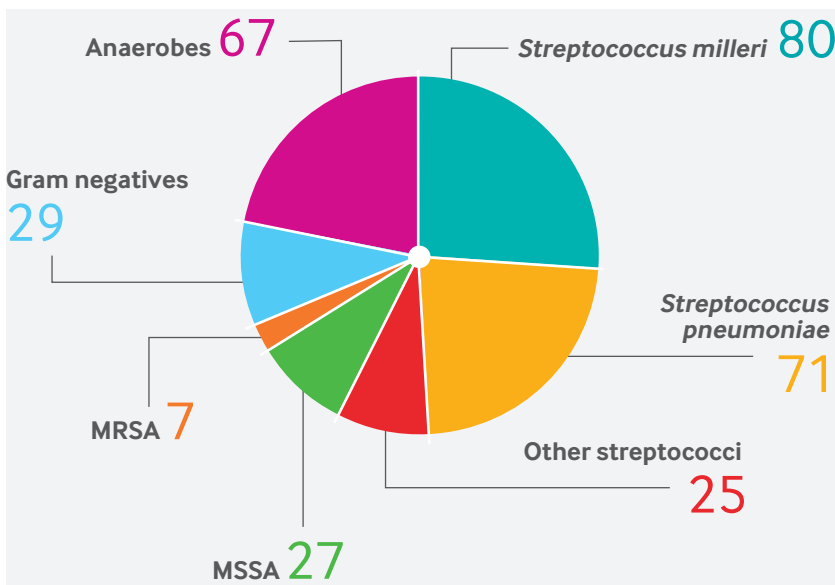


Fig 4 | Etiology of community acquired empyema determined by 16S rRNA sequencing. MRSA=meticillin resistant *Staphylococcus aureus*; MSSA=meticillin sensitive *Staph aureus*. From Maskell et al⁵⁹

allowing overgrowth of one or more of the resident flora. This concept may partially explain the high proportion of cases that are culture negative despite aggressive diagnosis.¹⁹ A hint that “normal” flora may be the cause of CAP comes from molecular diagnosis of community acquired empyema: “normal flora” *Streptococcus* spp cause a larger proportion than *S pneumoniae* (fig 4).⁵⁹

The most likely cause of this dysbiosis is antecedent or concomitant viral respiratory tract infection. The enigmatic but frequent association of human rhinovirus infection with clinical CAP may be explained by this phenomenon. Whether antibiotics help or hinder a return to the normal lung microbiome pattern in these cases is unclear. Possibly, ultrashort courses of antibiotic, such as a single dose of ceftriaxone, may be sufficient for clinical cure. Daptomycin, an antibiotic that was subsequently shown to be inactivated by surfactant, was compared with ceftriaxone in a registration trial for a CAP indication.⁶⁰ Patients admitted to hospital with CAP were allowed to have up to 24 hours of therapy before randomization, which was usually a single dose of ceftriaxone. The clinical cure rate in the subgroup of 97 patients who received a single dose of a long acting antibiotic such as ceftriaxone was 91% compared with 88% in patients who received a seven day course of ceftriaxone (95% confidence interval for the difference between cure rates –6.1% to 11.5%). In 272 patients randomized to daptomycin without previous antibiotic treatment (essentially placebo treatment), the clinical cure rate was still 75%, although this was significantly lower than in the equivalent number who received a seven day course of ceftriaxone (95% confidence interval for difference –18.8% to –6.0%). These findings are consistent with findings of procalcitonin directed treatment in which 15% or more of patients with CAP were safely managed without antibiotics.^{61 62}

The advent of newer molecular diagnostic techniques may revolutionize the diagnosis of CAP. Nucleic acid amplification can dramatically increase the diagnostic

yield of good quality sputum.^{42 63} The biggest limitation of any new molecular diagnostic technique is the lack of a gold standard for comparison. However, the potential for deep sequencing of appropriate respiratory samples raises the possibility of determining the entire lung microbiome to validate other molecular techniques as well as to discover new bacterial or viral causes of CAP.

Optimal antibiotic management

As the causative pathogen of CAP is almost never known initially in either inpatients or outpatients, treatment is virtually always empiric. As delay in starting antibiotics is associated with worse outcomes for patients, treatment should be started as soon as possible after a diagnosis is made, preferably within three to four hours of presentation.¹¹

First line treatment for CAP varies from region to region but is generally a β lactam/macrolide combination or a respiratory fluoroquinolone for patients in hospital.¹¹ In the outpatient setting, monotherapy with a β lactam, macrolide, or tetracycline is generally recommended unless risk factors for antibiotic resistant pathogens are present, mainly recent use of the same antibiotic or a high prevalence of resistant isolates in the community. Respiratory fluoroquinolones are also widely used for outpatients in some countries, including the US, but from an antibiotic stewardship perspective, narrower coverage is clearly preferable.⁶⁴

The optimal treatment of severe CAP is severely limited by lack of prospective clinical trials. More than a dozen retrospective studies suggest that combination antibiotics, particularly a β lactam and a macrolide, improve survival for patients admitted to hospital with pneumococcal pneumonia, as well as all cause CAP, compared with monotherapy with a β lactam.⁶⁵ Whether a β lactam/macrolide combination is superior to fluoroquinolone monotherapy is less clear, with conflicting findings and insufficient data in patients with severe disease.⁶⁶ As introduction of macrolide combination therapy was associated with a substantial drop in mortality in CAP patients in the intensive care unit (ICU),⁶⁷ administrative databases consistently show lower mortality with macrolide combination therapy,⁶⁸⁻⁷⁰ and meta-analysis shows a beneficial mortality risk ratio of 0.75 (95% confidence interval 0.58 to 0.96; P=0.02) for macrolide combination therapy in critically ill patients,⁷¹ until high quality data from randomized controlled trials (RCTs) are available, this should be the standard of care in severe CAP.¹¹

Non-intensive care patients

Treatment of patients admitted to hospital but not to ICU is the most contentious area of management. Two recent prospective trials have attempted to resolve the debate about combination antibiotic therapy for non-ICU patients. A Swiss RCT in patients admitted to hospital with CAP compared β lactam monotherapy with the identical β lactam combined with a macrolide and aimed to show that monotherapy was not inferior to combination therapy.⁷² The primary endpoint was time to clinical stability,⁷³ probably the most clinically relevant endpoint as inpatient mortality in non-ICU patients should be very

low. The trial failed to show that monotherapy was non-inferior in terms of time to clinical stability; only 34% (97/289) of monotherapy patients had reached clinical stability at day seven of therapy compared with 41% (120/291) for combination therapy, with the upper limit of the one sided 95% confidence interval (13%) exceeding the pre-specified boundary of 8%. Although the event rates were low, additional safety problems (deaths, ICU transfer, readmissions) also favored combination therapy. By this criterion, if monotherapy was being introduced as a new therapy for CAP in hospital, it would not be approved by regulatory authorities.⁷⁴

The second RCT conducted in the Netherlands used a more public health based approach. Seven hospitals were cluster randomized and crossed over between three treatment regimens as the “standard” for a four month period. This large (656-888 patients in each group) study found no significant difference in 90 day mortality between patients given β lactam or fluoroquinolone monotherapy or β lactam/macrolide combination.⁷⁵ Described as a “pragmatic randomised controlled trial,” this trial design had several major flaws. About 25% of patients did not have radiologic evidence of pneumonia. Monotherapy and no antibiotics are standard care for acute exacerbations of obstructive lung disease and heart failure, respectively, the most common causes of suspected CAP with a negative chest radiograph. The pragmatic design allowed clinicians to deviate from the “standard” therapy: 39% of the β lactam “monotherapy” patients actually also received atypical coverage, and 12% of patients in the combination therapy group did not get a macrolide. The choice of antibiotics within class also varied: 24% of patients in the combination therapy arm received penicillin as their β lactam, whereas only 2% received this in the β lactam monotherapy arm. Penicillin was strongly discouraged in the β lactam monotherapy arm because of resistance problems: the addition of a macrolide would not necessarily overcome the penicillin resistance. Clearly, a gradient of efficacy and spectrum of activity exists between β lactams and possibly even between members of the same class such as cephalosporins.⁷⁶ Erythromycin was also given to 35% of patients in the combination therapy arm, rather than other macrolides. Given the stronger association with acute cardiac events for erythromycin than for other macrolides,⁷⁷⁻⁷⁸ this may bias results in a study with a 90 day mortality endpoint. In addition, the four month randomization blocks may lead to a differential in recruitment in the “non-respiratory season” from May to early October in the northern hemisphere. During this time, atypical pathogens cause a higher proportion of documented causes of CAP. In the Netherlands, other studies suggest that 40% of documented causes of CAP during this time are atypical bacterial pathogens, with an even higher proportion in younger patients.⁷⁹ However, the greatest problem with the study is the choice of 90 day mortality as the primary endpoint. For patients who are not admitted to the ICU, mortality from uncontrolled infection is unlikely,⁸⁰⁻⁸² so the ability of this endpoint to discriminate antibiotic treatment effects is unclear. Most patients with CAP either die of acute cardiovascular events while in hospital or after discharge or die of their chronic

comorbidities.⁷⁷⁻⁸⁴ Therefore, although important from a public health standpoint, this RCT does not clearly inform the decision of which antibiotic treatment is “best” for non-ICU patients in hospital.

These studies show that β lactam monotherapy can safely be given to many patients admitted to hospital but not to ICU. Macrolide monotherapy can also likely be effective for some patients, such as young patients during the non-respiratory season. However, for purposes of a standard default treatment regimen, a β lactam/macrolide combination or fluoroquinolone monotherapy gives the most reliable results. Focusing on avoiding macrolide combination or fluoroquinolone treatment of documented CAP for antibiotic stewardship reasons is likely to have a minimal effect compared with avoiding antibiotic treatment for febrile upper respiratory tract or urinary tract infections.⁶⁴

Healthcare associated pneumonia

A subgroup of CAP termed “healthcare associated pneumonia” (HCAP) was introduced in the 2005 ATS/IDSA pneumonia guidelines.⁸⁵ Two US based studies reported a subgroup of patients with a high prevalence of pathogens more in keeping with hospital acquired pneumonia than with CAP, in particular a high rate of identification of MRSA and *Pseudomonas aeruginosa*.⁸⁶ The major risk factors for HCAP were identified as nursing home residence, recent hospital admission, dialysis, and chronic wound care,⁸⁷ and the guidelines suggested consideration of empiric coverage of MRSA and *P aeruginosa* if these risk factors were present.⁸⁵

Since publication of the guidelines, widespread adoption of the HCAP concept without consideration of local epidemiology has led to a vast overuse of inappropriately broad spectrum antibiotics (particularly vancomycin and β lactam/ β lactamase combinations) despite little evidence that these are needed outside of major urban centers in the US.⁸⁸⁻⁹¹ The CDC EPIC study, which included some patients with risk factors for HCAP in two major urban centers, found less than 3% of cases with MRSA or *Pseudomonas*.¹⁹

In addition, retrospective analyses have shown that empiric treatment for patients with the original HCAP risk factors is associated with no better or even worse mortality than treatment with usual CAP therapy.⁹²⁻⁹⁴ A Japanese study with excellent microbiologic diagnosis showed that only 27% had pathogens resistant to the usual CAP drugs.⁹⁵ Box 2 lists risk factors for these pathogens. Importantly, two or three risk factors were needed before the frequency of resistant pathogens warranted treatment outside the usual CAP drugs. In patients in the lowest risk category (0-1 risk factors), use of broad spectrum antibiotics, theoretically given to prevent inappropriate initial therapy, was actually associated with higher mortality than when inappropriate therapy was actually delivered (fig 5). Also, the undue attention to multidrug resistant pathogens often results in dropping the macrolide from the combination, with the attendant excess mortality.

Consequently, many publications call for abandonment of the HCAP classification on the grounds that it has done more harm than good.⁸⁸⁻⁹⁶ Clinicians must be aware of their local ecology and whether studies identifying risk

Box 2 | Independent risk factors for pneumonia⁹⁵**CAP drug resistant pathogens**

- Hospital admission in previous 90 days
- Antibiotics in previous 90 days
- Gastric acid suppression
- Immunosuppression
- Enteral tube feedings
- Non-ambulatory status

MRSA only*

- Hospital admission in previous 90 days
- Antibiotics in previous 90 days
- Gastric acid suppression
- Chronic hemodialysis
- Previous MRSA colonization
- Congestive heart failure

*Should include at least one MRSA specific risk (bottom three bullet points).

CAP=community acquired pneumonia; MRSA=meticillin resistant *Staphylococcus aureus*

factors for pathogens not covered by standard empiric therapy for CAP are applicable to their own setting. Published evidence suggests that the number of hospitals where the prevalence of MRSA or *Pseudomonas* is high enough to justify empirically covering these organisms is low.^{19 49}

Corticosteroids

Recent meta-analyses sparked debate about the potential benefit of corticosteroids in the setting of severe CAP.⁹⁷⁻⁹⁹ Despite the strong perception that meta-analyses represent the highest level of evidence, they are highly dependent on the quality of the primary studies. In the case of corticosteroids for CAP, the findings of meta-analyses are seriously undermined by the primary studies. Only two primary studies showed significant improvement in a meaningful clinical outcome. One RCT of 23 patients with severe CAP who received a 200 mg bolus of hydrocortisone, then an infusion of 10 mg/h for seven days, were compared with 23 patients taking placebo.¹⁰⁰ No deaths occurred in the hydrocortisone group and only 26% needed mechanical ventilation, compared with 38% mortality and 65% ventilation with placebo ($P<0.001$ for both). An Egyptian single blind study of 80 patients found that mortality was significantly reduced in patients taking a similar solumedrol regimen versus placebo (four deaths versus six for placebo; $P<0.05$).¹⁰¹ As no other study, including larger studies using the same dosing regimen, has shown even remotely comparable benefits, these results are not considered generalizable.

Although corticosteroids regimens in studies in CAP are typically called “low dose,” in reality at least moderate doses—equivalent to 40 mg per day of prednisolone—are used. Not surprisingly, hyperglycemia is more common in patients receiving steroids. Concern has been raised that steroids may be associated with excess mortality in patients with pneumonia due to influenza pneumonia.^{102 103} A recent post hoc analysis of one of the steroid trials also suggested that the benefit “reduced time to clinical stability” was not seen in the group with proven pneumococcal disease,¹⁰⁴ raising further questions about the subgroup of patients who do benefit.

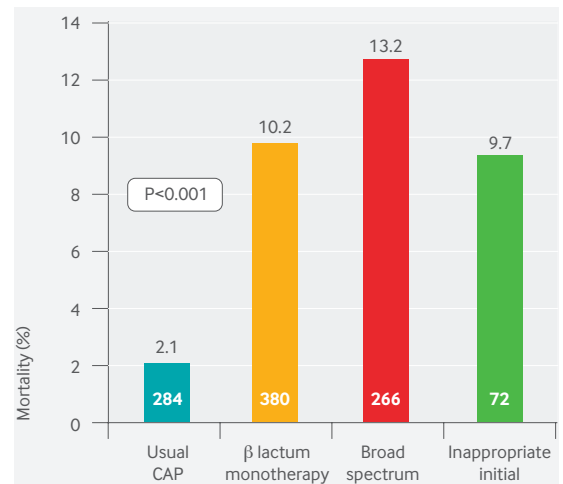


Fig 5 | Mortality in patients at low risk for resistant pathogens on basis of initial empiric antibiotic therapy. Numbers in bars represent patients. CAP=community acquired pneumonia. From Shindo et al⁹⁵

Corticosteroid therapy should not be used routinely in patients with CAP unless another indication is present (to treat a comorbid disease).¹⁰⁵ In patients with septic shock or who need mechanical ventilation and have high inflammatory markers, the risk-benefit balance may be in favor of steroids,¹⁰⁶ but further confirmatory studies are needed. Completion of a large Veterans Affairs Medical Center study of steroids for CAP will add additional information (ClinicalTrials.gov NCT01283009).

The role of biomarkers

A substantial amount of clinical judgment is needed in managing CAP patients, including selection of appropriate antibiotics, assignment of the appropriate location of care, and duration of treatment. An objective test result to reduce clinical uncertainty is appealing. A focus on biomarkers as an aid to clinical decision making has resulted, with procalcitonin being the best studied to date. Multiple studies have assessed the sensitivity and specificity of procalcitonin for the presence of bacterial infection in a variety of lower respiratory tract infections. However, we have focused only on data in patients admitted to hospital with CAP.

Various of cut-off values for procalcitonin have been assessed in the setting of CAP. At a threshold of 1.0 ng/mL, procalcitonin has a reasonably high predictive value for typical bacterial infection.^{107 108} However, in the context of withholding antibiotic therapy on the presumption of a viral infection, procalcitonin has several limitations. Firstly, procalcitonin is often not elevated in the setting of *Legionella* and *Mycoplasma* infections.¹⁰⁹⁻¹¹¹ Several studies also raise concern that procalcitonin has a poor sensitivity in the presence of mixed bacterial and viral infection.¹¹⁰⁻¹¹⁴

Only one interventional trial in the setting of CAP in adults attempted to withhold antibiotics on the basis of a low procalcitonin result.⁶¹ In this study, 22 of 43 patients with procalcitonin concentrations below 0.25 ng/mL had antibiotics withheld, although five subsequently had antibiotics started owing to a higher reading at six hours. No

adverse effects of withholding antibiotics were observed. On a risk-benefit basis, the data for using a procalcitonin result to withhold antibiotic therapy in patients with CAP remains insufficient.

Another suggested role of procalcitonin is to reduce the duration of antibiotic therapy. Several studies using a serial procalcitonin measurement protocol to determine duration of antibiotic treatment have shown a reduced length of therapy, but in all cases the standard therapy arm had durations well beyond seven days,⁶¹⁻¹¹⁵ much longer than recommended in current guidelines. Therefore, procalcitonin is likely to be useful only in guiding duration of antibiotic therapy in settings where clinicians routinely exceed the recommended duration.

A potential role for procalcitonin in predicting which patients with CAP are at risk of adverse outcomes has been proposed.¹¹⁶⁻¹¹⁹ The benefit of procalcitonin, or any other biomarker, over existing validated clinical scoring systems such as the pneumonia severity index, ATS major and minor criteria, or CURB-65 remains unclear.¹²⁰⁻¹²¹

CAP and acute cardiac disease

Several studies in patients admitted with CAP show an increased risk of acute myocardial infarction,⁷⁷⁻¹²⁶ cardiac arrhythmia,⁷⁷⁻¹²⁷ and new onset heart failure.¹²⁸ Up to 20% of patients with bacteremic pneumococcal pneumonia can experience these cardiovascular complications.¹²⁴ This risk is not just acute but extends outwards for several months to years afterwards.¹²⁸⁻¹³⁰

Mechanisms by which CAP provokes cardiovascular events are not clear; however, several possibilities exist.¹³¹ Infection induces a procoagulant state, including increases in clotting factors, platelet numbers, and platelet activation. The degree of platelet activation has been associated with the risk of acute myocardial infarction in the setting of pneumonia.¹³² Increases in heart rate and myocardial oxygen consumption may provoke arrhythmia in damaged or vulnerable myocardium. Endothelial dysfunction and inflammatory cytokines may also precipitate acute plaque rupture.¹³³

Treatment with antiplatelet agents may be associated with better outcomes in patients with pneumonia in both prospective interventional and retrospective observational studies.¹²⁵⁻¹³⁵ A dose higher than 100 mg of aspirin seems to be needed, as this dose failed to reduce mortality or myocardial infarction rates in pneumonia and did not lower platelet activation markers.¹³² Retrospective data suggest that clopidogrel may be more effective than aspirin at reducing myocardial events in the setting of pneumonia,¹³⁶ and ticagrelor even more so.¹³⁷ Further studies are needed to determine which patients benefit and the optimal agent, dose, and duration of therapy.

Longer term outcomes

Many studies have documented that patients who survive CAP have a significantly greater mortality rate of up to 30% over the next two to five years,⁸³⁻¹⁴³ even in those without comorbid diseases.¹³⁸ In the first 90 days after discharge from hospital, mortality is highest in patients with the highest markers of inflammation¹⁴⁴: higher levels of pro-adrenomedullin and pro-atrial natriuretic

peptide also seem to predict increased long term mortality risk.¹⁴²⁻¹⁴³ The cause of the excess mortality is multifactorial, but increased cardiac disease including myocardial infarction and heart failure is a prominent reason.¹²⁸⁻¹³⁰

Although knowledge of how to reduce the burden of mortality and morbidity in CAP survivors is limited, measures to reduce acute cardiac injury at the time of pneumonia are logical. Given the increasing awareness that pneumonia clearly has long term health implications, this represents a critical area for research and a major paradigm shift for physicians treating patients with CAP.

CAP “bundle of care”

Sepsis now has a well defined bundle of care associated with optimizing patient outcomes.¹⁴⁵ Bundles are more than just a group of interventions; they are a process designed so that each patient receives the optimal care every time, and the interventions are designed on the basis of the best available evidence. A pilot program in Britain showed a reduction in 30 day inpatient mortality from 13.6% to 8.8% with the use of a CAP care bundle of timely antibiotic administration and guideline concordant therapy.¹⁴⁶

On the basis of the available data, the following interventions should be considered in a CAP care bundle:

- Use of a validated CAP severity score to aid in clinical evaluation and determination of site of care.¹⁴⁷⁻¹⁴⁸
- Rapid empiric antibiotic administration with a β lactam and macrolide (ideally within three hours of presentation).⁶⁷⁻¹⁵⁰
- Rapid resuscitation, including adequate fluid resuscitation, correcting electrolyte disturbances and hyperglycemia, thromboembolic prophylaxis, and managing hypoxia appropriately.¹⁴⁵
- Encouraging early ambulation.¹⁵⁰⁻¹⁵²
- Tackling cardiovascular risk factors, including consideration of starting or continuing aspirin at a dose shown to be effective.

Guidelines

Many countries and professional societies publish their own CAP guidelines. In addition to the frequently cited ATS/IDSA guidelines,¹¹ other widely used guidelines include the British, Canadian,¹⁵³ Spanish,¹⁵⁴ Dutch,¹⁵⁵ Chinese,¹⁵⁶ and Japanese guidelines.¹⁵⁷

Guidelines are appropriately written to reflect local healthcare systems and to meet different needs. Guidelines from professional societies were initially developed to reflect expert opinion for use by clinicians who were less experienced.¹¹⁻¹⁵⁸ Some, such as the ATS/IDSA guidelines, have evolved into prescriptive rules for third party payers and public reporting measures,¹⁵⁹⁻¹⁶⁰ which in turn forces changes in methods and priorities.

The major differences observed between guidelines primarily reflect these different purposes and different healthcare systems and relate to those areas with an uncertain evidence base discussed above. For example, a large proportion of patients admitted to hospital with CAP have very low acuity and could equally well be managed as outpatients. National Institute for Health and Care Excellence guidelines emphasize that these patients are

equivalent to outpatients as regards etiology and therefore should be treated with monotherapy.¹⁵⁸ The average length of hospital admission for CAP in non-ICU patients in the Netherlands is six days,⁷⁵ compared with only three in the US.¹⁹ This allows a longer observation period for β lactam monotherapy with the ability to add atypical coverage for poor responders in the Netherlands,⁷⁵ whereas the need for subsequent return to the hospital for failure of monotherapy in the US would have financial and public reporting consequences.

Emerging treatments

Search of ClinicalTrials.gov (PNEUMONIA and COMMUNITY and ACQUIRED) finds 266 studies with 58 open protocols. Emerging treatments include three main categories. The first and most likely area to have an early clinical impact is new diagnostic platforms. The benefit of a greater proportion of and earlier switch to specific therapy rather than the current overwhelming use of empiric antibiotic therapy, even for viral pneumonia, will need to be studied. CAP is an easier indication than hospital acquired pneumonia/ventilator associated pneumonia (HAP/VAP) for new diagnostics, given a more limited bacterial spectrum and fewer problems with resistance.

The second area is additional antimicrobials. The most exciting is the spectrum of antivirals other than neuraminidase inhibitors and for pathogens other than influenza that are entering phase II and III clinical trials. The new antibiotics being studied are likely to have a more limited clinical impact. Most seek to replace quinolones or macrolides, for antibiotic stewardship reasons for the first and for emerging but still extremely variable resistance problems for the second. Given the very high success rates for the current standard, mostly generic antibiotic treatment of outpatients and inpatients outside ICU with CAP, the few new classes of antibiotics have a greater future for HAP/VAP if the spectrum allows.

The third area is severe CAP, for which a more rapid diagnosis of its causes or newer antibiotics have lower potential benefit and adjunctive therapy is likely to affect mortality and morbidity to a greater extent. In addition to steroids, novel therapeutic agents being studied include compounds that neutralize toxins, including pneumolysin,¹⁶¹ monoclonal or polyclonal antibodies to specific pathogens,^{162,163} and immunoglobulin therapy.¹⁶⁴ Most deaths directly attributable to CAP involve either septic shock or severe hypoxemic respiratory failure in patients with either viruses or antibiotic susceptible bacteria; improvement in ICU support technologies are therefore a different but very valid strategy to improve outcomes of CAP. Gas exchange support while avoiding injurious ventilator strategies via extracorporeal carbon dioxide removal and a new generation of extracorporeal membrane oxygenators are being studied.¹⁶⁵ In addition, new strategies for vasopressor support can buy time for antibiotic therapy to work.¹⁶⁶

Conclusions

CAP remains a highly prevalent and serious disease with acute and long term adverse health outcomes. Imaging technology is changing our understanding of CAP, and

RESEARCH QUESTIONS

- Is thoracic ultrasonography equivalent to computed tomography for diagnostic imaging of pneumonia?
- Can molecular techniques accurately determine the cause in culture negative cases of community acquired pneumonia (CAP)?
- Is short course antibiotic therapy (<24 hours) safe in patients with documented viral pneumonia? Can procalcitonin correctly identify those patients?
- Can primary prevention of atherosclerotic plaque rupture (eg, statin, low dose aspirin) decrease mortality after admission for CAP?
- What, if any, adjunctive therapy can decrease the mortality of severe CAP in previously healthy people.

better diagnostic tools are changing our understanding of the pathogens causing CAP. A clearer picture is emerging of the optimal bundle of care for patients with CAP, with an increasing body of evidence supporting multiple interventions. Optimal treatment remains controversial, and well designed trials are still needed, particularly in severe disease; however, evidence favors a macrolide/ β lactam combination for severe disease. Corticosteroids may have a net positive effect in some patients with severe disease, but the evidence base remains weak and further studies are needed to define the subset of patients who benefit. Despite much research, procalcitonin has no clear role in CAP unless physicians are routinely using more than seven days of antibiotic therapy. The most substantial change in focus in CAP is awareness of the significant increase in acute cardiovascular events and the long term adverse health outcomes in survivors, and research is urgently needed to determine the optimal approach to these complications. Combining all available research, the group of interventions likely to produce the best possible outcomes for patients is becoming clearer and should be considered as a therapeutic bundle to optimize care of patients with CAP.

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- 1 World Health Organization. The top 10 causes of death. 2017. <http://www.who.int/mediacentre/factsheets/fs310/en/>.
- 2 GBD 2013 Mortality and Causes of Death Collaborators. Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;385:117-71. doi:10.1016/S0140-6736(14)61682-2 pmid:25530442.
- 3 Global Burden of Disease Study 2013 Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 301 acute and chronic diseases and injuries in 188 countries, 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2015;386:743-800. doi:10.1016/S0140-6736(15)60692-4 pmid:26063472.
- 4 Weingarten SR, Lloyd L, Chiou CF, Braunstein GD. Do subspecialists working outside of their specialty provide less efficient and lower-quality care to hospitalized patients than do primary care physicians? *Arch Intern Med* 2002;162:527-32. doi:10.1001/archinte.162.5.527 pmid:11871920.
- 5 Schappert SM, Burt CW. Ambulatory care visits to physician offices, hospital outpatient departments, and emergency departments: United States, 2001-02. *Vital Health Stat 13* 2006;(159):1-66. pmid:16471269.
- 6 Weiss AJ, Wier LM, Stocks C, Blanchard J. Overview of Emergency Department Visits in the United States, 2011: Statistical Brief #174. 2014. <https://www.hcup-us.ahrq.gov/reports/statbriefs/sb174-Emergency-Department-Visits-Overview.pdf>.

- 7 Pfunter A, Wier LM, Stocks C. Most frequent conditions in U.S. hospitals, 2011: Statistical Brief #162. 2013. <https://www.hcup-us.ahrq.gov/reports/statbriefs/sb162.pdf>.
- 8 Carratalà J, Rosón B, Fernández-Sevilla A, Alcaide F, Gudiol F. Bacteremic pneumonia in neutropenic patients with cancer: causes, empirical antibiotic therapy, and outcome. *Arch Intern Med* 1998;158:868-72. doi:10.1001/archinte.158.8.868 pmid:9570172.
- 9 Cillóniz C, Torres A, Manzardo C, et al. Community-Acquired Pneumococcal Pneumonia in Virologically Suppressed HIV-Infected Adult Patients: A Matched Case-Control Study. *Chest* 2017;S0012-3692(17)30368-9. pmid:28302496.
- 10 Curtis JR, Yang S, Patkar NM, et al. Risk of hospitalized bacterial infections associated with biologic treatment among US veterans with rheumatoid arthritis. *Arthritis Care Res (Hoboken)* 2014;66:990-7. doi:10.1002/acr.22281 pmid:24470378.
- 11 Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis* 2007;44(Suppl 2):S27-72. doi:10.1086/511159 pmid:17278083.
- 12 Kalil AC, Metersky ML, Klompas M, et al. Management of Adults With Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clin Infect Dis* 2016;63:e61-111. doi:10.1093/cid/ciw353 pmid:27418577.
- 13 Bradley JS, Byington CL, Shah SS, et al. Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the Pediatric Infectious Diseases Society and the Infectious Diseases Society of America. *Clin Infect Dis* 2011;53:e25-76. doi:10.1093/cid/cir531 pmid:21880587.
- 14 Jain S, Williams DJ, Arnold SR, et al. CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization among U.S. children. *N Engl J Med* 2015;372:835-45. doi:10.1056/NEJMoa1405870 pmid:25714161.
- 15 Kochanek KD, Murphy SL, Xu J, Tejada-Verba B. Deaths: Final Data for 2014. *Natl Vital Stat Rep* 2016;65:1-122. pmid:27378572.
- 16 Boersma F, Van Den Brink W, Deeg DJ, Eefsting JA, Van Tilburg W. Survival in a population-based cohort of dementia patients: predictors and causes of mortality. *Int J Geriatr Psychiatry* 1999;14:748-53. doi:10.1002/(SICI)1099-1166(199909)14:9<748::AID-GPS3>3.0.CO;2-H pmid:10479746.
- 17 Mitchell SL, Teno JM, Kiely DK, et al. The clinical course of advanced dementia. *N Engl J Med* 2009;361:1529-38. doi:10.1056/NEJMoa0902234 pmid:19828530.
- 18 Sharafkhaneh A, Spiegelman AM, Main K, Tavakoli-Tabasi S, Lan C, Musher D. Mortality in Patients Admitted for Concurrent COPD Exacerbation and Pneumonia. *COPD* 2017;14:23-9. doi:10.1080/15412555.2016.1220513 pmid:27661473.
- 19 Jain S, Self WH, Wunderink RG, et al. CDC EPIC Study Team. Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. *N Engl J Med* 2015;373:415-27. doi:10.1056/NEJMoa1500245 pmid:26172429.
- 20 Smith SB, Ruhnke GW, Weiss CH, Waterer GW, Wunderink RG. Trends in pathogens among patients hospitalized for pneumonia from 1993 to 2011. *JAMA Intern Med* 2014;174:1837-9. doi:10.1001/jamainternmed.2014.4344 pmid:25200864.
- 21 Marston BJ, Plouffe JF, File TM Jr, et al. The Community-Based Pneumonia Incidence Study Group. Incidence of community-acquired pneumonia requiring hospitalization. Results of a population-based active surveillance study in Ohio. *Arch Intern Med* 1997;157:1709-18. doi:10.1001/archinte.1997.00440360129015 pmid:9250232.
- 22 Takahashi K, Suzuki M, Minh N, et al. The incidence and aetiology of hospitalised community-acquired pneumonia among Vietnamese adults: a prospective surveillance in Central Vietnam. *BMC Infect Dis* 2013;13:296. doi:10.1186/1471-2334-13-296 pmid:23815298.
- 23 Zingone F, Abdul Sultan A, Crooks CJ, Tata LJ, Giacci C, West J. The risk of community-acquired pneumonia among 9803 patients with coeliac disease compared to the general population: a cohort study. *Aliment Pharmacol Ther* 2016;44:57-67. doi:10.1111/apt.13652 pmid:27151603.
- 24 Quan TP, Fawcett NJ, Wrightson JM, et al. Infections in Oxfordshire Research Database (IORD). Increasing burden of community-acquired pneumonia leading to hospitalisation, 1998-2014. *Thorax* 2016;71:535-42. doi:10.1136/thoraxjnl-2015-207688 pmid:26888780.
- 25 Azmi S, Aljunied SM, Maimaiti N, et al. Assessing the burden of pneumonia using administrative data from Malaysia, Indonesia, and the Philippines. *Int J Infect Dis* 2016;49:87-93. doi:10.1016/j.ijid.2016.05.021 pmid:27235085.
- 26 Rozenbaum MH, Mangan MJ, Huijts SM, van der Werf TS, Postma MJ. Incidence, direct costs and duration of hospitalization of patients hospitalized with community acquired pneumonia: A nationwide retrospective claims database analysis. *Vaccine* 2015;33:3193-9. doi:10.1016/j.vaccine.2015.05.001 pmid:25981488.
- 27 Ewig S, Birchner N, Strauss R, et al. New perspectives on community-acquired pneumonia in 388 406 patients. Results from a nationwide mandatory performance measurement programme in healthcare quality. *Thorax* 2009;64:1062-9. doi:10.1136/thx.2008.109785 pmid:19454409.
- 28 Hopstaken RM, Witbraad T, van Engelshoven JM, Dinant GJ. Inter-observer variation in the interpretation of chest radiographs for pneumonia in community-acquired lower respiratory tract infections. *Clin Radiol* 2004;59:743-52. doi:10.1016/j.crad.2004.01.011 pmid:15262550.
- 29 Albaum MN, Hill LC, Murphy M, et al. PORT Investigators. Interobserver reliability of the chest radiograph in community-acquired pneumonia. *Chest* 1996;110:343-50. doi:10.1378/chest.110.2.343 pmid:8697831.
- 30 Boersma WG, Daniels JM, Löwenberg A, Boeve WJ, van de Jagt EJ. Reliability of radiographic findings and the relation to etiologic agents in community-acquired pneumonia. *Respir Med* 2006;100:926-32. doi:10.1016/j.rmed.2005.06.018 pmid:16337367.
- 31 Campbell SG, Murray DD, Hawass A, Urquhart D, Ackroyd-Stolarz S, Maxwell D. Agreement between emergency physician diagnosis and radiologist reports in patients discharged from an emergency department with community-acquired pneumonia. *Emerg Radiol* 2005;11:242-6. doi:10.1007/s10140-005-0413-4 pmid:16133615.
- 32 Kanwar M, Brar N, Khatib R, Fakhri MG. Misdiagnosis of community-acquired pneumonia and inappropriate utilization of antibiotics: side effects of the 4-h antibiotic administration rule. *Chest* 2007;131:1865-9. doi:10.1378/chest.07-0164 pmid:17400668.
- 33 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;192:974-82. doi:10.1164/rccm.201501-00170C pmid:26168322.
- 34 Self WH, Courtney DM, McNaughton CD, Wunderink RG, Kline JA. High discordance of chest x-ray and computed tomography for detection of pulmonary opacities in ED patients: implications for diagnosing pneumonia. *Am J Emerg Med* 2013;31:401-5. doi:10.1016/j.ajem.2012.08.041 pmid:23083885.
- 35 Syrjala H, Broas M, Ohtonen P, Jartti A, Pääkkö E. Chest magnetic resonance imaging for pneumonia diagnosis in outpatients with lower respiratory tract infection. *Eur Respir J* 2017;49:1601303. doi:10.1183/13993003.01303-2016 pmid:27811069.
- 36 Neroladaki A, Botsikas D, Boudabbous S, Becker CD, Montet X. Computed tomography of the chest with model-based iterative reconstruction using a radiation exposure similar to chest X-ray examination: preliminary observations. *Eur Radiol* 2013;23:360-6. doi:10.1007/s00330-012-2627-7 pmid:22892722.
- 37 Ohana M, Ludes C, Schaal M, et al. [What future for chest x-ray against ultra-low-dose computed tomography?]. *Rev Pneumol Clin* 2017;73:3-12. doi:10.1016/j.pneumo.2016.09.007 pmid:27956084.
- 38 Llamas-Álvarez AM, Tenza-Lozano EM, Latour-Pérez J. Accuracy of Lung Ultrasonography in the Diagnosis of Pneumonia in Adults: Systematic Review and Meta-Analysis. *Chest* 2017;151:374-82. doi:10.1016/j.chest.2016.10.039 pmid:27818332.
- 39 Bonten MJ, Huijts SM, Bolkenbaas M, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. *N Engl J Med* 2015;372:1114-25. doi:10.1056/NEJMoa1408544 pmid:25785969.
- 40 Jacobs MR, Good CE, Bajaksouzian S, Windau AR. Emergence of Streptococcus pneumoniae serotypes 19A, 6C, and 22F and serogroup 15 in Cleveland, Ohio, in relation to introduction of the protein-conjugated pneumococcal vaccine. *Clin Infect Dis* 2008;47:1388-95. doi:10.1086/592972 pmid:18959493.
- 41 Griffin MR, Zhu Y, Moore MR, Whitney CG, Grijalva CG. U.S. hospitalizations for pneumonia after a decade of pneumococcal vaccination. *N Engl J Med* 2013;369:155-63. doi:10.1056/NEJMoa1209165 pmid:23841730.
- 42 Holter JC, Müller F, Bjørngang O, et al. Etiology of community-acquired pneumonia and diagnostic yields of microbiological methods: a 3-year prospective study in Norway. *BMC Infect Dis* 2015;15:64. doi:10.1186/s12879-015-0803-5 pmid:25887603.
- 43 Franz A, Adams O, Willems R, et al. Correlation of viral load of respiratory pathogens and co-infections with disease severity in children hospitalized for lower respiratory tract infection. *J Clin Virol* 2010;48:239-45. doi:10.1016/j.jcv.2010.05.007 pmid:20646956.
- 44 van den Hoogen BG, de Jong JC, Groen J, et al. A newly discovered human pneumovirus isolated from young children with respiratory tract disease. *Nat Med* 2001;7:19-24. doi:10.1038/89098 pmid:11385510.
- 45 Cilloniz C, Albert RK, Liapikou A, et al. The Effect of Macrolide Resistance on the Presentation and Outcome of Patients Hospitalized for Streptococcus pneumoniae Pneumonia. *Am J Respir Crit Care Med* 2015;191:1265-72. doi:10.1164/rccm.201502-02120C pmid:25807239.
- 46 Pereyre S, Goret J, Bébéar C. Mycoplasma pneumoniae: Current Knowledge on Macrolide Resistance and Treatment. *Front Microbiol* 2016;7:974. doi:10.3389/fmicb.2016.00974 pmid:27446015.
- 47 Defres S, Marwick C, Nathwani D. MRSA as a cause of lung infection including airway infection, community-acquired pneumonia and hospital-acquired pneumonia. *Eur Respir J* 2009;34:1470-6. doi:10.1183/09031936.00122309 pmid:19948913.
- 48 Self WH, Wunderink RG, Williams DJ, et al. Staphylococcus aureus Community-acquired Pneumonia: Prevalence, Clinical Characteristics, and Outcomes. *Clin Infect Dis* 2016;63:300-9. doi:10.1093/cid/ciw300 pmid:27161775.
- 49 Metersky ML, Frei CR, Mortensen EM. Predictors of Pseudomonas and methicillin-resistant Staphylococcus aureus in hospitalized patients with healthcare-associated pneumonia. *Respirology* 2016;21:157-63. doi:10.1111/resp.12651 pmid:26682638.
- 50 Lobo LJ, Reed KD, Wunderink RG. Expanded clinical presentation of community-acquired methicillin-resistant Staphylococcus aureus pneumonia. *Chest* 2010;138:130-6. doi:10.1378/chest.09-1562 pmid:20173050.

- 51 Gillet Y, Issartel B, Vanhems P, et al. Association between *Staphylococcus aureus* strains carrying gene for Panton-Valentine leukocidin and highly lethal necrotising pneumonia in young immunocompetent patients. *Lancet* 2002;359:753-9. doi:10.1016/S0140-6736(02)07877-7 pmid:11888586.
- 52 Brown ML, O'Hara FP, Close NM, et al. Prevalence and sequence variation of panton-valentine leukocidin in methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* strains in the United States. *J Clin Microbiol* 2012;50:86-90. doi:10.1128/JCM.05564-11 pmid:22090402.
- 53 Hidron AI, Low CE, Honig EG, Blumberg HM. Emergence of community-acquired methicillin-resistant *Staphylococcus aureus* strain USA300 as a cause of necrotising community-onset pneumonia. *Lancet Infect Dis* 2009;9:384-92. doi:10.1016/S1473-3099(09)70133-1 pmid:19467478.
- 54 Trevino SE, Pence MA, Marschall J, Kollef MH, Babcock HM, Burnham CD. Rapid MRSA PCR on respiratory specimens from ventilated patients with suspected pneumonia: a tool to facilitate antimicrobial stewardship. *Eur J Clin Microbiol Infect Dis* 2017;36:879-85. doi:10.1007/s10096-016-2876-5 pmid:28004323.
- 55 Baby N, Faust AC, Smith T, Sheperd LA, Knoll L, Goodman EL. Nasal Methicillin-Resistant *Staphylococcus aureus* (MRSA) PCR Testing Reduces the Duration of MRSA-Targeted Therapy in Patients with Suspected MRSA Pneumonia. *Antimicrob Agents Chemother* 2017;61:e02432-16. doi:10.1128/AAC.02432-16 pmid:28137813.
- 56 Einarsson GG, Comer DM, McIlreavey L, et al. Community dynamics and the lower airway microbiota in stable chronic obstructive pulmonary disease, smokers and healthy non-smokers. *Thorax* 2016;71:795-803. doi:10.1136/thoraxjnl-2015-207235 pmid:27146202.
- 57 Charlson ES, Bittinger K, Haas AR, et al. Topographical continuity of bacterial populations in the healthy human respiratory tract. *Am J Respir Crit Care Med* 2011;184:957-63. doi:10.1164/rccm.201104-0655OC pmid:21680950.
- 58 Dickson RP, Erb-Downward JR, Huffnagle GB. Towards an ecology of the lung: new conceptual models of pulmonary microbiology and pneumonia pathogenesis. *Lancet Respir Med* 2014;2:238-46. doi:10.1016/S2213-2600(14)70028-1 pmid:24621685.
- 59 Maskell NA, Batt S, Hedley EL, Davies CW, Gillespie SH, Davies RJ. The bacteriology of pleural infection by genetic and standard methods and its mortality significance. *Am J Respir Crit Care Med* 2006;174:817-23. doi:10.1164/rccm.200601-074OC pmid:16840746.
- 60 Pertel PE, Bernardo P, Fogarty C, et al. Effects of prior effective therapy on the efficacy of daptomycin and ceftriaxone for the treatment of community-acquired pneumonia. *Clin Infect Dis* 2008;46:1142-51. doi:10.1086/533441 pmid:18444848.
- 61 Christ-Crain M, Stolz D, Bingisser R, et al. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med* 2006;174:84-93. doi:10.1164/rccm.200512-1922OC pmid:16603606.
- 62 Schuetz P, Christ-Crain M, Thomann R, et al. ProHOSP Study Group. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. *JAMA* 2009;302:1059-66. doi:10.1001/jama.2009.1297 pmid:19738090.
- 63 Diaz MH, Cross KE, Benitez AJ, et al. Identification of Bacterial and Viral Codetections With *Mycoplasma pneumoniae* Using the TaqMan Array Card in Patients Hospitalized With Community-Acquired Pneumonia. *Open Forum Infect Dis* 2016;3:ofw071. doi:10.1093/ofid/ofw071 pmid:27191004.
- 64 Weiss K, Tillotson GS. Fluoroquinolones for respiratory infection: too valuable to overuse (and too valuable to misuse). *Chest* 2002;122:1102-3, author reply 1103. doi:10.1378/chest.122.3.1102 pmid:12226065.
- 65 Nie W, Li B, Xiu Q. β -Lactam/macrolide dual therapy versus β -lactam monotherapy for the treatment of community-acquired pneumonia in adults: a systematic review and meta-analysis. *J Antimicrob Chemother* 2014;69:1441-6. doi:10.1093/jac/dku033 pmid:24535276.
- 66 Vardakas KZ, Siempos II, Grammatikos A, Athanassa Z, Korbila IP, Falagas ME. Respiratory fluoroquinolones for the treatment of community-acquired pneumonia: a meta-analysis of randomized controlled trials. *CMAJ* 2008;179:1269-77. doi:10.1503/cmaj.080358 pmid:19047608.
- 67 Gattarello S, Borgatta B, Solé-Violán J, et al. Community-Acquired Pneumonia en la Unidad de Cuidados Intensivos II Study Investigators*. Decrease in mortality in severe community-acquired pneumococcal pneumonia: impact of improving antibiotic strategies (2000-2013). *Chest* 2014;146:22-31. doi:10.1378/chest.13-1531 pmid:24371840.
- 68 Brown RB, Iannini P, Gross P, Kunkel M. Impact of initial antibiotic choice on clinical outcomes in community-acquired pneumonia: analysis of a hospital claims-made database. *Chest* 2003;123:1503-11. doi:10.1378/chest.123.5.1503 pmid:12740267.
- 69 Meehan TP, Fine MJ, Krumholz HM, et al. Quality of care, process, and outcomes in elderly patients with pneumonia. *JAMA* 1997;278:2080-4. doi:10.1001/jama.1997.03550230056037 pmid:9403422.
- 70 Metersky ML, Ma A, Houck PM, Bratzler DW. Antibiotics for bacteremic pneumonia: Improved outcomes with macrolides but not fluoroquinolones. *Chest* 2007;131:466-73. doi:10.1378/chest.06-1426 pmid:17296649.
- 71 Sligl W, Asadi L, Eurich DT, Tjosvold L, Marrie TJ, Majumdar SR. Macrolides and mortality in critically ill patients with community-acquired pneumonia: a systematic review and meta-analysis. *Crit Care Med* 2014;42:420-32. doi:10.1097/CCM.0b013e3182a66b9b pmid:24158175.
- 72 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;174:1894-901. doi:10.1001/jamainternmed.2014.4887 pmid:25286173.
- 73 Halm EA, Fine MJ, Marrie TJ, et al. Time to clinical stability in patients hospitalized with community-acquired pneumonia: implications for practice guidelines. *JAMA* 1998;279:1452-7. doi:10.1001/jama.279.18.1452 pmid:9600479.
- 74 Mandell LA, Waterer GW. Empirical Therapy of Community-Acquired Pneumonia: Advancing Evidence or Just More Doubt? *JAMA* 2015;314:396-7. doi:10.1001/jama.2015.3858 pmid:26219057.
- 75 Postma DF, van Werkhoven CH, van Elden LJ, et al. CAP-START Study Group. Antibiotic treatment strategies for community-acquired pneumonia in adults. *N Engl J Med* 2015;372:1312-23. doi:10.1056/NEJMoa1406330 pmid:25830421.
- 76 Taboada M, Melnick D, Iaconis JP, et al. Ceftazidime fosamil versus ceftriaxone for the treatment of community-acquired pneumonia: individual patient data meta-analysis of randomized controlled trials. *J Antimicrob Chemother* 2016;71:862-70. doi:10.1093/jac/ckv415 pmid:26702925.
- 77 Perry TW, Pugh MJ, Waterer GW, et al. Incidence of cardiovascular events after hospital admission for pneumonia. *Am J Med* 2011;124:244-51. doi:10.1016/j.amjmed.2010.11.014 pmid:21396508.
- 78 Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. *N Engl J Med* 2012;366:1881-90. doi:10.1056/NEJMoa1003833 pmid:22591294.
- 79 Raeven VM, Spoorenberg SM, Boersma WG, et al. Alkmaar study group Ovidius study group. Atypical aetiology in patients hospitalised with community-acquired pneumonia is associated with age, gender and season; a data-analysis on four Dutch cohorts. *BMC Infect Dis* 2016;16:299. doi:10.1186/s12879-016-1641-9 pmid:27317257.
- 80 Mortensen EM, Coley CM, Singer DE, et al. Causes of death for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study. *Arch Intern Med* 2002;162:1059-64. doi:10.1001/archinte.162.9.1059 pmid:11996618.
- 81 Simpson JC, Macfarlane JT, Watson J, Woodhead MA. British Thoracic Society Research Committee and Public Health Laboratory Service. A national confidential enquiry into community acquired pneumonia deaths in young adults in England and Wales. *Thorax* 2000;55:1040-5. doi:10.1136/thorax.55.12.1040 pmid:11083890.
- 82 Metersky ML, Waterer G, Nsa W, Bratzler DW. Predictors of in-hospital vs postdischarge mortality in pneumonia. *Chest* 2012;142:476-81. doi:10.1378/chest.11-2393 pmid:22383662.
- 83 Mortensen EM, Kapoor WN, Chang CC, Fine MJ. Assessment of mortality after long-term follow-up of patients with community-acquired pneumonia. *Clin Infect Dis* 2003;37:1617-24. doi:10.1086/379712 pmid:14689342.
- 84 Carr GE, Yuen TC, McConville JF, et al. American Heart Association's Get With the Guidelines-Resuscitation (National Registry of CPR) Investigators. Early cardiac arrest in patients hospitalized with pneumonia: a report from the American Heart Association's Get With The Guidelines-Resuscitation Program. *Chest* 2012;141:1528-36. doi:10.1378/chest.11-1547 pmid:22194592.
- 85 American Thoracic Society Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2005;171:388-416. doi:10.1164/rccm.200405-644ST pmid:15699079.
- 86 Kollef MH, Shorr A, Tabak YP, Gupta V, Liu LZ, Johannes RS. Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia. *Chest* 2005;128:3854-62. doi:10.1378/chest.128.6.3854 pmid:16354854.
- 87 Shorr AF, Zilberberg MD, Micek ST, Kollef MH. Prediction of infection due to antibiotic-resistant bacteria by select risk factors for health care-associated pneumonia. *Arch Intern Med* 2008;168:2205-10. doi:10.1001/archinte.168.20.2205 pmid:19001196.
- 88 Chalmers JD, Rother C, Salih W, Ewig S. Healthcare-associated pneumonia does not accurately identify potentially resistant pathogens: a systematic review and meta-analysis. *Clin Infect Dis* 2014;58:330-9. doi:10.1093/cid/cit734 pmid:24270053.
- 89 Dobler CC, Waterer G. Healthcare-associated pneumonia: a US disease or relevant to the Asia Pacific, too? *Respirology* 2013;18:923-32. doi:10.1111/resp.12132 pmid:23714303.
- 90 Ewig S, Welte T. Adding fuel to the flames? It is time to leave HCAP. *Respir Med* 2012;106:1309-10. doi:10.1016/j.rmed.2012.07.002 pmid:22795985.
- 91 Webb BJ, Dascomb K, Stenehjem E, Dean N. Predicting risk of drug-resistant organisms in pneumonia: moving beyond the HCAP model. *Respir Med* 2015;109:1-10. doi:10.1016/j.rmed.2014.10.017 pmid:25468412.
- 92 Chen JJ, Slater LN, Kurdgelashvili G, Husain KO, Gentry CA. Outcomes of health care-associated pneumonia empirically treated with guideline-concordant regimens versus community-acquired pneumonia guideline-concordant regimens for patients admitted to acute care wards from home. *Ann Pharmacother* 2013;47:9-19. doi:10.1345/aph.1R322 pmid:23324506.
- 93 Webb BJ, Dangerfield BS, Pasha JS, Agrwal N, Vikram HR. Guideline-concordant antibiotic therapy and clinical outcomes in healthcare-associated pneumonia. *Respir Med* 2012;106:1606-12. doi:10.1016/j.rmed.2012.08.003 pmid:22917808.

- 94 Grenier C, Pépin J, Nault V, et al. Impact of guideline-consistent therapy on outcome of patients with healthcare-associated and community-acquired pneumonia. *J Antimicrob Chemother* 2011;66:1617-24. doi:10.1093/jac/ckr176 pmid:21586592.
- 95 Shindo Y, Ito R, Kobayashi D, et al. Risk factors for drug-resistant pathogens in community-acquired and healthcare-associated pneumonia. *Am J Respir Crit Care Med* 2013;188:985-95. doi:10.1164/rccm.201301-00790C pmid:23855620.
- 96 Shindo Y, Hasegawa Y. Emerging problems regarding severity assessment and treatment strategies for patients with pneumonia: controversies surrounding the HCAP concept. *Intern Emerg Med* 2011;6:389-91. doi:10.1007/s11739-011-0623-6 pmid:21590438.
- 97 Siemieniuk RA, Meade MO, Alonso-Coello P, et al. Corticosteroid Therapy for Patients Hospitalized With Community-Acquired Pneumonia: A Systematic Review and Meta-analysis. *Ann Intern Med* 2015;163:519-28. doi:10.7326/M15-0715 pmid:26258555.
- 98 Horita N, Otsuka T, Haranaga S, et al. Adjunctive Systemic Corticosteroids for Hospitalized Community-Acquired Pneumonia: Systematic Review and Meta-Analysis 2015 Update. *Sci Rep* 2015;5:14061. doi:10.1038/srep14061 pmid:26374694.
- 99 Chen LP, Chen JH, Chen Y, Wu C, Yang XH. Efficacy and safety of glucocorticoids in the treatment of community-acquired pneumonia: A meta-analysis of randomized controlled trials. *World J Emerg Med* 2015;6:172-8. doi:10.5847/wjem.j.1920-8642.2015.03.002 pmid:26401176.
- 100 Confalonieri M, Urbino R, Potena A, et al. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. *Am J Respir Crit Care Med* 2005;171:242-8. doi:10.1164/rccm.200406-8080C pmid:15557131.
- 101 Nafae R, Ragab M, Amany F, Rashed S. Adjuvant role of corticosteroids in the treatment of community-acquired pneumonia. *Egypt J Chest Dis Tuberc* 2013;62:439-45 doi:10.1016/j.ejcd.2013.03.009.
- 102 Yang JW, Fan LC, Miao XY, et al. Corticosteroids for the treatment of human infection with influenza virus: a systematic review and meta-analysis. *Clin Microbiol Infect* 2015;21:956-63. doi:10.1016/j.cmi.2015.06.022 pmid:26123860.
- 103 Cao B, Gao H, Zhou B, et al. Adjuvant Corticosteroid Treatment in Adults With Influenza A (H7N9) Viral Pneumonia. *Crit Care Med* 2016;44:e318-28. doi:10.1097/CCM.0000000000001616 pmid:26934144.
- 104 Wirz SA, Blum CA, Schuetz P, et al. for the STEP Study Group. Pathogen- and antibiotic-specific effects of prednisone in community-acquired pneumonia. *Eur Respir J* 2016;48:1150-9. doi:10.1183/13993003.00474-2016 pmid:27471201.
- 105 Wunderink RG. Corticosteroids for severe community-acquired pneumonia: not for everyone. *JAMA* 2015;313:673-4. doi:10.1001/jama.2015.115 pmid:25688777.
- 106 Torres A, Sibila O, Ferrer M, et al. Effect of corticosteroids on treatment failure among hospitalized patients with severe community-acquired pneumonia and high inflammatory response: a randomized clinical trial. *JAMA* 2015;313:677-86. doi:10.1001/jama.2015.88 pmid:25688779.
- 107 Pfister R, Kochanek M, Leygeber T, et al. Procalcitonin for diagnosis of bacterial pneumonia in critically ill patients during 2009 H1N1 influenza pandemic: a prospective cohort study, systematic review and individual patient data meta-analysis. *Crit Care* 2014;18:R44. doi:10.1186/cc13760 pmid:24612487.
- 108 Wu MH, Lin CC, Huang SL, et al. Can procalcitonin tests aid in identifying bacterial infections associated with influenza pneumonia? A systematic review and meta-analysis. *Influenza Other Respir Viruses* 2013;7:349-55. doi:10.1111/ir.1250-2659.2012.00386.x pmid:22672284.
- 109 Musher DM, Roig IL, Cazares G, Stager CE, Logan N, Safar H. Can an etiologic agent be identified in adults who are hospitalized for community-acquired pneumonia: results of a one-year study. *J Infect* 2013;67:11-8. doi:10.1016/j.jinf.2013.03.003 pmid:23523447.
- 110 Krüger S, Ewig S, Papassotiropoulos J, et al. CAPNETZ Study Group. Inflammatory parameters predict etiologic patterns but do not allow for individual prediction of etiology in patients with CAP: results from the German competence network CAPNETZ. *Respir Res* 2009;10:65. doi:10.1186/1465-9921-10-65 pmid:19594893.
- 111 Bellmann-Weiler R, Auserwinkler M, Kurz K, Theurl I, Weiss G. Clinical potential of C-reactive protein and procalcitonin serum concentrations to guide differential diagnosis and clinical management of pneumococcal and Legionella pneumonia. *J Clin Microbiol* 2010;48:1915-7. doi:10.1128/JCM.01348-09 pmid:20220163.
- 112 Musher DM, Bebk SP, Roig IL. Serum procalcitonin level, viral polymerase chain reaction analysis, and lower respiratory tract infection. *J Infect Dis* 2014;209:631-3. doi:10.1093/infdis/jit579 pmid:24218499.
- 113 Bello S, Mincholé E, Fandos S, et al. Inflammatory response in mixed viral-bacterial community-acquired pneumonia. *BMC Pulm Med* 2014;14:123. doi:10.1186/1471-2466-14-123 pmid:25073709.
- 114 Ahn S, Kim WY, Kim SH, et al. Role of procalcitonin and C-reactive protein in differentiation of mixed bacterial infection from 2009 H1N1 viral pneumonia. *Influenza Other Respir Viruses* 2011;5:398-403. doi:10.1111/ir.1250-2659.2011.00244.x pmid:21668682.
- 115 Long W, Deng XQ, Tang JG, et al. [The value of serum procalcitonin in treatment of community acquired pneumonia in outpatient]. *Zhonghua Nei Ke Za Zhi* 2009;48:216-9. pmid:19576090.
- 116 Ito A, Ishida T, Tachibana H, Ito Y, Takaiwa T. Serial procalcitonin levels for predicting prognosis in community-acquired pneumonia. *Respirology* 2016;21:1459-64. doi:10.1111/resp.12846 pmid:27398948.
- 117 Self WH, Grijalva CG, Williams DJ, et al. Procalcitonin as an Early Marker of the Need for Invasive Respiratory or Vasopressor Support in Adults With Community-Acquired Pneumonia. *Chest* 2016;150:819-28. doi:10.1016/j.chest.2016.04.010 pmid:27107491.
- 118 Fernandes L, Arora AS, Mesquita AM. Role of Semi-quantitative Serum Procalcitonin in Assessing Prognosis of Community Acquired Bacterial Pneumonia Compared to PORT PSI, CURB-65 and CRB-65. *J Clin Diagn Res* 2015;9:OC01-04. pmid:26393153.
- 119 Tamura M, Watanabe M, Nakajima A, et al. Serial quantification of procalcitonin (PCT) predicts clinical outcome and prognosis in patients with community-acquired pneumonia (CAP). *J Infect Chemother* 2014;20:97-103. doi:10.1016/j.jiac.2013.09.005 pmid:24462441.
- 120 Viasus D, Del Rio-Pertuz G, Simonetti AF, et al. Biomarkers for predicting short-term mortality in community-acquired pneumonia: A systematic review and meta-analysis. *J Infect* 2016;72:273-82. doi:10.1016/j.jinf.2016.01.002 pmid:26777314.
- 121 Lim HF, Phua J, Mukhopadhyay A, et al. IDSA/ATS minor criteria aid pre-intensive care unit resuscitation in severe community-acquired pneumonia. *Eur Respir J* 2014;43:852-62. doi:10.1183/09031936.00081713 pmid:24176994.
- 122 Ramirez J, Aliberti S, Mirsaedi M, et al. Acute myocardial infarction in hospitalized patients with community-acquired pneumonia. *Clin Infect Dis* 2008;47:182-7. doi:10.1086/589246 pmid:18533841.
- 123 Corrales-Medina VF, Serpa J, Rueda AM, et al. Acute bacterial pneumonia is associated with the occurrence of acute coronary syndromes. *Medicine (Baltimore)* 2009;88:154-9. doi:10.1097/MD.0b013e3181a692f0 pmid:19440118.
- 124 Musher DM, Rueda AM, Kaka AS, Mapara SM. The association between pneumococcal pneumonia and acute cardiac events. *Clin Infect Dis* 2007;45:158-65. doi:10.1086/518849 pmid:17578773.
- 125 Oz F, Gul S, Kaya MG, et al. Does aspirin use prevent acute coronary syndrome in patients with pneumonia: multicenter prospective randomized trial. *Coron Artery Dis* 2013;24:231-7. doi:10.1097/MCA.0b013e3182835d7610 pmid:23283029.
- 126 Viasus D, Garcia-Vidal C, Manresa F, Dorca J, Gudiol F, Carratalà J. Risk stratification and prognosis of acute cardiac events in hospitalized adults with community-acquired pneumonia. *J Infect* 2013;66:27-33. doi:10.1016/j.jinf.2012.09.003 pmid:22981899.
- 127 Soto-Gomez N, Anzueto A, Waterer GW, Restrepo MI, Mortensen EM. Pneumonia: an arrhythmogenic disease? *Am J Med* 2013;126:43-8. doi:10.1016/j.amjmed.2012.08.005 pmid:23177550.
- 128 Corrales-Medina VF, Taljaard M, Yende S, et al. Intermediate and long-term risk of new-onset heart failure after hospitalization for pneumonia in elderly adults. *Am Heart J* 2015;170:306-12. doi:10.1016/j.ahj.2015.04.028 pmid:26299228.
- 129 Corrales-Medina VF, Alvarez KN, Weissfeld LA, et al. Association between hospitalization for pneumonia and subsequent risk of cardiovascular disease. *JAMA* 2015;313:264-74. doi:10.1001/jama.2014.18229 pmid:25602997.
- 130 Koivula I, Stén M, Mäkelä PH. Prognosis after community-acquired pneumonia in the elderly: a population-based 12-year follow-up study. *Arch Intern Med* 1999;159:1550-5. doi:10.1001/archinte.159.14.1550 pmid:10421277.
- 131 Singanayagam A, Singanayagam A, Elder DH, Chalmers JD. Is community-acquired pneumonia an independent risk factor for cardiovascular disease? *Eur Respir J* 2012;39:187-96. doi:10.1183/09031936.000491111 pmid:21737556.
- 132 Cangemi R, Casciaro M, Rossi E, et al. SIXTUS Study Group SIXTUS Study Group. Platelet activation is associated with myocardial infarction in patients with pneumonia. *J Am Coll Cardiol* 2014;64:1917-25. doi:10.1016/j.jacc.2014.07.985 pmid:25444147.
- 133 Aukrust P, Sandberg WJ, Otterdal K, et al. Tumor necrosis factor superfamily molecules in acute coronary syndromes. *Ann Med* 2011;43:90-103. doi:10.3109/07853890.2010.523711 pmid:21039303.
- 134 Falcone M, Russo A, Cangemi R, et al. Lower mortality rate in elderly patients with community-onset pneumonia on treatment with aspirin. *J Am Heart Assoc* 2015;4:e001595. doi:10.1161/JAHA.114.001595 pmid:25564372.
- 135 Falcone M, Russo A, Farcomeni A, et al. Septic shock from community-onset pneumonia: is there a role for aspirin plus macrolides combination? *Intensive Care Med* 2016;42:301-2. doi:10.1007/s00134-015-4139-9 pmid:26585791.
- 136 Gross AK, Dunn SP, Feola DJ, et al. Clopidogrel treatment and the incidence and severity of community acquired pneumonia in a cohort study and meta-analysis of antiplatelet therapy in pneumonia and critical illness. *J Thromb Thrombolysis* 2013;35:147-54. doi:10.1007/s11239-012-0833-4 pmid:23124575.
- 137 Storey RF, James SK, Siegbahn A, et al. Lower mortality following pulmonary adverse events and sepsis with ticagrelor compared to clopidogrel in the PLATO study. *Platelets* 2014;25:517-25. doi:10.3109/09537104.2013.842965 pmid:24127651.
- 138 Waterer GW, Kessler LA, Wunderink RG. Medium-term survival after hospitalization with community-acquired pneumonia. *Am J Respir Crit Care Med* 2004;169:910-4. doi:10.1164/rccm.200310-14480C pmid:14693672.

- 139 Sandvall B, Rueda AM, Musher DM. Long-term survival following pneumococcal pneumonia. *Clin Infect Dis* 2013;56:1145-6. doi:10.1093/cid/cis1207 pmid:23300240.
- 140 Dick A, Liu H, Zwanziger J, et al. Long-term survival and healthcare utilization outcomes attributable to sepsis and pneumonia. *BMC Health Serv Res* 2012;12:432. doi:10.1186/1472-6963-12-432 pmid:23181764.
- 141 Vögeli A, Ottiger M, Meier MA, et al. Admission levels of asymmetric and symmetric dimethylarginine predict long-term outcome in patients with community-acquired pneumonia. *Respir Res* 2017;18:25. doi:10.1186/s12931-017-0502-4 pmid:28114935.
- 142 Alan M, Grolmund E, Kutz A, et al. ProHOSP study group. Clinical risk scores and blood biomarkers as predictors of long-term outcome in patients with community-acquired pneumonia: a 6-year prospective follow-up study. *J Intern Med* 2015;278:174-84. doi:10.1111/joim.12341 pmid:25529395.
- 143 Guertler C, Wirz B, Christ-Crain M, Zimmerli W, Mueller B, Schuetz P. Inflammatory responses predict long-term mortality risk in community-acquired pneumonia. *Eur Respir J* 2011;37:1439-46. doi:10.1183/09031936.00121510 pmid:21071473.
- 144 Yende S, D'Angelo G, Kellum JA, et al. GenIMS Investigators. Inflammatory markers at hospital discharge predict subsequent mortality after pneumonia and sepsis. *Am J Respir Crit Care Med* 2008;177:1242-7. doi:10.1164/rccm.200712-1777OC pmid:18369199.
- 145 Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. *Intensive Care Med* 2017;43:304-77. doi:10.1007/s00134-017-4683-6 pmid:28101605.
- 146 Lim WS, Rodrigo C, Turner AM, Welham S, Calvert JM. British Thoracic Society. British Thoracic Society community-acquired pneumonia care bundle: results of a national implementation project. *Thorax* 2016;71:288-90. doi:10.1136/thoraxjnl-2015-206834 pmid:26197815.
- 147 Renaud B, Coma E, Hayon J, et al. PNEUMOCOM study investigators. Investigation of the ability of the Pneumonia Severity Index to accurately predict clinically relevant outcomes: a European study. *Clin Microbiol Infect* 2007;13:923-31. doi:10.1111/j.1469-0691.2007.01772.x pmid:17617186.
- 148 Vohra AS, Tak HJ, Shah MB, Meltzer DO, Ruhnke GW. Intensive Care Unit Admission With Community-Acquired Pneumonia. *Am J Med Sci* 2015;350:380-6. doi:10.1097/MAJ.0000000000000568 pmid:26445305.
- 149 Menéndez R, Torres A, Reyes S, et al. Initial management of pneumonia and sepsis: factors associated with improved outcome. *Eur Respir J* 2012;39:156-62. doi:10.1183/09031936.00188710 pmid:21828033.
- 150 Carratalà J, García-Vidal C, Ortega L, et al. Effect of a 3-step critical pathway to reduce duration of intravenous antibiotic therapy and length of stay in community-acquired pneumonia: a randomized controlled trial. *Arch Intern Med* 2012;172:922-8. doi:10.1001/archinternmed.2012.1690 pmid:22732747.
- 151 Mundy LM, Leet TL, Darst K, Schnitzler MA, Dunagan WC. Early mobilization of patients hospitalized with community-acquired pneumonia. *Chest* 2003;124:883-9. doi:10.1378/chest.124.3.883 pmid:12970012.
- 152 José A, Dal Corso S. Inpatient rehabilitation improves functional capacity, peripheral muscle strength and quality of life in patients with community-acquired pneumonia: a randomised trial. *J Physiother* 2016;62:96-102. doi:10.1016/j.jphys.2016.02.014 pmid:26996093.
- 153 Mandell LA, Marrie TJ, Grossman RF, Chow AW, Hyland RH. The Canadian Community-Acquired Pneumonia Working Group. Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by the Canadian Infectious Diseases Society and the Canadian Thoracic Society. *Clin Infect Dis* 2000;31:383-421. doi:10.1086/3139599 pmid:10987698.
- 154 Alfageme I, Aspa J, Bello S, et al. Grupo de Estudio de la Neumonía Adquirida en la Comunidad. Área de Tuberculosis e Infecciones Respiratorias (TIR)-SEPAR Spanish Society of Pulmonology and Thoracic Surgery (SEPAR). [Guidelines for the diagnosis and management of community-acquired pneumonia]. *Arch Bronconeumol* 2005;41:272-89. doi:10.1155/2005.41.272-89 pmid:15919009.
- 155 Wiersinga WJ, Bonten MJ, Boersma WG, et al. Dutch Working Party on Antibiotic Policy Dutch Association of Chest Physicians. SWAB/NVALT (Dutch Working Party on Antibiotic Policy and Dutch Association of Chest Physicians) guidelines on the management of community-acquired pneumonia in adults. *Neth J Med* 2012;70:90-101. doi:10.1016/j.njm.2012.07.001 pmid:22418758.
- 156 Qu JM, Cao B. [Guidelines for the diagnosis and treatment of adult community acquired pneumonia in China (2016 Edition)]. *Zhonghua Jie He He Hu Xi Za Zhi* 2016;39:241-2. doi:10.1370169.
- 157 Miyashita N, Matsushima T, Oka M. Japanese Respiratory Society. The JRS guidelines for the management of community-acquired pneumonia in adults: an update and new recommendations. *Intern Med* 2006;45:419-28. doi:10.2169/internalmedicine.45.1691 pmid:16679695.
- 158 Eccles S, Pincus C, Higgins B, Woodhead M. Guideline Development Group. Diagnosis and management of community and hospital acquired pneumonia in adults: summary of NICE guidance. *BMJ* 2014;349:g6722. doi:10.1136/bmj.g6722 pmid:25471702.
- 159 Lilford R, Pronovost P. Using hospital mortality rates to judge hospital performance: a bad idea that just won't go away. *BMJ* 2010;340:c2016. doi:10.1136/bmj.c2016 pmid:20406861.
- 160 Kupfer JM. The morality of using mortality as a financial incentive: unintended consequences and implications for acute hospital care. *JAMA* 2013;309:2213-4. doi:10.1001/jama.2013.5009 pmid:23736729.
- 161 Anderson R, Feldman C. Pneumolysin as a potential therapeutic target in severe pneumococcal disease. *J Infect* 2017;4:527-44. doi:10.1016/j.jinf.2017.03.005 pmid:28322888.
- 162 Rouha H, Badarau A, Visram ZC, et al. Five birds, one stone: neutralization of α -hemolysin and 4 bi-component leukocidins of *Staphylococcus aureus* with a single human monoclonal antibody. *MAbs* 2015;7:243-54. doi:10.4161/19420862.2014.985132 pmid:25252328.
- 163 Yu XQ, Robbie GJ, Wu Y, et al. Safety, Tolerability, and Pharmacokinetics of MEDI4893, an Investigational, Extended-Half-Life, Anti-*Staphylococcus aureus* Alpha-Toxin Human Monoclonal Antibody, in Healthy Adults. *Antimicrob Agents Chemother* 2016;61:e01020-16. doi:10.1128/AAC.01020-16 pmid:27795368.
- 164 Welte T, Dellinger RP, Ebel H, et al. Concept for a study design in patients with severe community-acquired pneumonia: A randomised controlled trial with a novel IGM-enriched immunoglobulin preparation - The CIGMA study. *Respir Med* 2015;109:758-67. doi:10.1016/j.rmed.2015.03.008 pmid:25887136.
- 165 Combes A, Pesenti A, Ranieri VM. Fifty Years of Research in ARDS. Is Extracorporeal Circulation the Future of Acute Respiratory Distress Syndrome Management? *Am J Respir Crit Care Med* 2017;195:1161-70. doi:10.1164/rccm.201701-0217CP pmid:28459322.
- 166 Khanna A, English SW, Wang XS, et al. ATHOS-3 Investigators. Angiotensin II for the Treatment of Vasodilatory Shock. *N Engl J Med* 2017. doi:10.1056/NEJMoa1704154 pmid:28528561.