Review Article

Management of severe community acquired pneumonia in the emergency department

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Abstract: Severe community acquired pneumonia (CAP) is a medical emergency and thus, it should be managed as such. Prompt recognition of severe CAP and timely, appropriate initiation of antimicrobials and execution of resuscitation bundles in the emergency department (ED) will save lives and reduce the burden of disease in hospital and patient morbidities downstream. However, these are complex multifaceted interventions which require deliberate planning and design, careful implementation sustained by close monitoring and maintenance efforts. Widespread implementation of these measures is further hampered by uncertainties, controversies and debates between researchers on the evidential basis for the precise stratification of CAP disease severity and the relative merits of different treatment options. Physicians in the ED however should not hesitate to act but apply the best available evidence in the local settings heuristically with pragmatic interventions to improve critical outcomes for patients with severe CAP. In this regard, we have performed a qualitative, aggregative type review of the management of severe CAP in the ED concluding each section with a realist synthesis. We describe the implementation of resuscitation bundles in the management of severe CAP in the ED and the process of sustaining such an enterprise.

Keywords: Septic shock; respiratory failure; severe community acquired pneumonia (CAP); emergency; quality improvement

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Introduction

"*Knowing is not enough*; *we must apply*. *Willing is not enough*; *we must do*." by Johann Wolfgang von Goethe (1).

The world is witnessing a high and rising burden of community acquired pneumonia (CAP). (2). Severe CAP is a very serious and dangerous illness which is associated with high mortality (3,4). Despite advances in emergency and critical care, severe CAP is attended by poor clinical outcomes and a rising mortality (4,5). In contrast to severe CAP, survival from severe sepsis and shock has improved markedly in recent years, especially in more developed countries (6-8). This is most likely related to early recognition and aggressive resuscitation practices at the emergency room espoused and promoted by the surviving sepsis campaigns (9). In particular, the early goal directed therapy (EDGT) of septic shock is now so well adopted and executed by emergency and critical care teams in routine practice that recent controlled studies failed to detect any difference in clinical performance and patient outcomes between intervention and control groups (10-12). Sadly, this is not the case in severe CAP where mortality rates remain and high there is no agreement among experts and practitioners on many pivotal points regarding its diagnosis and management (13-15).

Rather than re-iterating these differences in opinions,

we believe that, just like acute myocardial infarction and thrombotic strokes, severe CAP is a medical emergency and thus, should be managed as such (16,17). Finding practical solutions in a setting of factual uncertainty is at the root of clinical reasoning and medical decision making (18). Aristotle named this process of practical wisdom and decisions making "phronesis" which identifies, in a complex or ambiguous situation, the best rather than the right decision (where best equates to good and right equates to correct in the sense of true or approved) (19). Where prescriptive or optimal recommendations are not possible, applying an educated heuristic and taking the best possible or "satisficing" option, as described by Herbert Simon, may be expedient and appropriate (20-23). Thus, we will describe the management of severe CAP in the emergency department (ED) based on the best avail evidence and our own experience over the past decade in improving the acute care of this major medical emergency.

Methods

The management of severe CAP involve complex multifaceted interventions which are not easily amenable to prospectively randomised head-to-head clinical trials. Thus, a formal quantitative meta-analysis and systematic review of severe CAP management may not yield meaning or useful results. Instead, we have performed a qualitative, aggregative type review according to the process of realist synthesis (24,25). This is based primarily upon relevant publications on the management of CAP in MEDLINE in the past 10 years. A search limited to "adults +19 years", "clinical trials", "reviews" and "systematic review" yielded eligible 197 publications. This was supplemented by publications from our own research files (17,26-31).

The diagnosis of CAP

It is now widely recognized that errors in the diagnosis of CAP in the ED are very common (32,33). The frequency of misdiagnosing CAP varies with the reference standard and in one high quality prospective study, it was reported that, after CT examinations, more than half the patient had to be reclassified (34,35). Patients miscoded as having pneumonia but who did not actually have CAP tend to have more comorbidities, significantly fewer respiratory symptoms (fever, cough, dyspnoea, pleuritic pain), more constitutional symptoms (general deterioration, falls) and lower mortality (36). Conversely, CAP which was missed on plain radiographs but detected on CT was not any less severe (37). Bedside ultrasound might be an alternative imaging method especially in children (38). While the current diagnosis of CAP is less than optimal, yet we have no clear evidence to suggest that a more accurate diagnosis will improve patient outcomes. It is also unlikely that there will be wide application of much more expensive imaging methods like the CT scan in the near future. Nevertheless, a careful systematic search for the source of infection and its control in all septic patients in the ED is required. This is crucial for the early and effective treatment of CAP and other causes of sepsis (39).

Early recognition of severe CAP

The search for the ideal CAP severity score has generated the most research energies, volume of publications and controversy (40-44). This journey however has made little progress in the 20 years since the first CAP scores were promulgated (40,41,43,44). In recent years this process has included a concerted search for new biomarkers which have failed to improve on either clinical CAP severity scores or patient outcomes (45). Thus, we do not recommend the routine testing of biomarkers in CAP unless it is firmly linked to a structured care program directed at improving patient outcomes with a robust audit process to evaluate its effectiveness (46).

An unintended, indirect, unappreciated and yet real consequence of this uncertainty regarding which is the best CAP severity score is delay in the application of life saving treatment steps especially in the large group of patients who do not present, initially, with easily recognizable, frank and salient features of life-threatening CAP. Now, after over two decades of intense research, there is an emerging realization and consensus that perhaps no clinic score will ever be perfect and that our research efforts should be shifted towards interventions and implementation steps which will actually improve patient outcomes instead of just receiver operating curve statistics (47).

We recommend that despite its limitations, which have been extensively reviewed in the literature, the 2007 ATS/IDSA criteria for CAP severity should be the basis for identify patients as having life-threatening CAP and who need immediate resuscitation in the ED and consideration for early admission to an intensive care unit. (27,29,42,43,48). We suggest that, in addition, just as in sepsis treatment protocols, in patients with CAP, the

serum lactate levels should be measured and monitored for clearance even in non-hypotensive patients as an indication for fluid resuscitation and evaluation of its effectiveness (29,49-51). In cases of uncertainty, evaluation of all available information, careful clinical judgment in consultation with colleagues, close monitoring following initiation of prompt aggressive and resuscitation bundles on a trial and error basis is necessary.

The identification of pathogens in severe CAP

There is a large body of research on pathogens and their rapid identification using advanced molecular techniques in CAP (30,52-57). However, the promise of effective pathogen directed and timely antimicrobial treatment of CAP arising from these studies have not yet being realized (58). Thus, it is more pertinent, in the current situation, to be aware of the prevalence of the resistant bacteria causing CAP using conventional methods (59). In particular, regional differences in antibiotic-resistant pathogens in patients with pneumonia should be reflected in local CAP management guidelines (60-62). We recommend that in patients with severe CAP, respiratory tract secretions and blood cultures should be routinely tested for common bacterial pathogens using conventional methods and that in countries tuberculosis (TB) is prevalent, this should include mycobacterial smear, rapid molecular tests and cultures of the sputum. Where available, it may be desirable to test for pneumococcal and legionella antigens in the urine, but this should not be the basis for a strategy of pathogen targeted selection of initial antimicrobial treatment. We do not recommend routine testing for viral respiratory pathogens but this may be indicated in some patients and situations for infection control and public health surveillance purposes.

Early antimicrobial administration

The causative organisms for respiratory infections vary with the climate change, environmental influences, human migratory factors and socio-economic factors (63-66). Hence the aetiology of severe CAP may differ in various regions globally (31). Epidemiological studies have identified the most common pathogens causing severe CAP which include *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, *Hemophilus influenzae*, *Pseudomonas aeruginosa* and other gram-negative bacilli, *Legionella spp*, respiratory viruses such as influenza A and B and co-infections. *Burkhorderia pseudomallei* and *Mycobacteria tuberculosis* are endemic in the tropics and are associated with high mortality (26,67-70).

Major international guidelines recommend a beta- lactam (such as amoxicillin-clavulanate, ampicillin-sulbactam, cefotaxime or ceftriaxone) in combination with a macrolide (azithromycin or clarithromycin). In penicillin allergic individuals, a fluoroquinolone (such as levofloxacin) with aztreonam could be the alternative (42). Several systematic reviews and meta-analyses which studied macrolides in combination with beta-lactams in hospitalized non-critically ill CAP revealed conflicting results. Some showed a reduction in mortality with macrolide combination therapy while others did not (71-73). In critically ill patients with severe CAP, combination macrolide therapy seemed to confer a mortality benefit (70). The use of fluoroquinolone monotherapy or in combination with beta-lactams which did not show superiority to combination therapy with beta-lactams and macrolides (74,75). The use of fluoroquinolones was also shown to delay diagnosis of TB and should be avoided if TB was suspected (76).

Prompt administration of appropriate antibiotics in sepsis and septic shock had been associated with improved outcomes in observational studies (19,20,77,78). The Surviving Sepsis Campaign 2016 made a strong recommendation in administering antimicrobial treatment within an hour for sepsis and septic shock (9). The recommendation was further supported by recent studies published in SCAP that early administration of antibiotics and combination therapy are associated with improved intensive care survival (79-82). Some studies suggest that pre-hospital delays with antibiotic administration was associated with worsened survival and antibiotic therapy prior to hospital admission was associated with reduced incidence of septic shock and need for mechanical ventilation in patients with CAP (82). The efficacy of pre-hospital treatment needs further investigations as a recent trial of antibiotic administration in the ambulance did not show any benefits (83).

The patients with severe CAP who received guideline concordant antibiotics had improved mortality (84-87). This result differed from patients with health-care associated pneumonia (HCAP). This form of pneumonia was defined by the American guidelines in 2005 in patients who were from the community that had frequent healthcare contacts (88). The guidelines proposed administering broad spectrum antibiotics to target multidrug resistant pathogens. In a recent meta-analysis by Chalmers *et al.* showed that the HCAP definition did not accurately identify resistant pathogens or had an increased mortality compared to

CAP (89). Administration of these broad-spectrum antibiotics based on these criteria did not improve outcomes (90,91). In 2011, the Europeans had declared HCAP to be a clinically irrelevant entity in European guidelines for lower respiratory tract infections and recommended to look for risk factors for multi-drug resistant pathogens (92). Recent observational studies performed in CAP revealed less than 10% of the cohort isolated multidrug resistant pathogens such as *Pseudomonas aeruginosa*, *Methicillin-resistant Staphylococcus aureus* (MRSA) and *Enterobacteriaceae* extended spectrum beta lactamase (PES) (93,94). Seasonal influenza remains a global health burden. Early empirical antiviral treatment may reduce mortality in hospitalised and critically ill patients as evident by the H1N1 influenza pandemic in 2009 (95,96).

Based on the current available evidence, we recommend early administration of appropriate antibiotics at the ED within an hour on identification of severe CAP in accordance to local epidemiology and resistance patterns (97). Combination therapy with macrolides would be favored instead of fluquinolones in TB endemic areas. We recommend empiric coverage to include melioidosis in areas that are endemic. We do not recommend empiric anti-pseudomonal or MRSA therapy in patients without risk factors for multi-drug resistant pathogens and in areas with low incidence of PES organisms or those with the HCAP appellation.

Hemodynamic resuscitation

In a landmark study in 2001, Rivers *et al.* demonstrated that EDGT reduced mortality in patients with severe sepsis and septic shock from 46.5% to 30.5% (10). The EDGT bundle consist of lactate measurements, fluid resuscitation to titrate central venous pressure 8–12 mmHg, vasopressor therapy to titrate mean arterial pressure (MAP) of 65 mmHg, red blood cell transfusion and inotropes to target the central venous oxygen ($ScVO_2$) above 70 mmHg (29). This formed the premise of sepsis resuscitation guidelines. Observational studies from the surviving sepsis campaign database reported improved mortality with those hospitals with high adherence to sepsis bundles (98). In 2014–2015, there were three large randomized control trials (the PROCESS, ARISE and ProMISE) performed which did not show EDGT had improved outcomes compared to usual care. The patients in the EDGT arms required increased intensive care unit utilization, more vasopressors and central venous line insertions (12). These trials probably demonstrated that there was an overall improvement in sepsis resuscitation over the last decade.

The Surviving Sepsis Campaign 2016 recommended an initial fluid bolus of 30 mL/kg in sepsis induced hypotension and subsequent fluid boluses to be titrated according to hemodynamic status. This recommendation was shown to be safe in the PROCESS, ARISE and ProMISE trials as the patients recruited had at least 2 L of fluid before randomization (12). In a recent observational study Leisman *et al.* showed that early initiation of fluid resuscitation within 30 minutes was associated with reduction of mortality and initial volumes of 20–35mL/kg was associated with improved lactate clearance and lower risk of mechanical ventilation (99). However, the optimal fluid strategy in resuscitation is still subjected to controversy as Marik *et al.* demonstrated that administration of more than 5 L of fluid in the first 24 hours was associated with increased mortality regardless of severity of illness and increase hospital costs (100). This observation is supported by two randomized studies which showed that aggressive fluid loading was associated with increased risk of death (101,102).

Although these trials and guidelines are in sepsis, we recommend adopting these strategies in severe CAP as a significant proportion of the patients recruited in these trials had a pulmonary source of sepsis. We recommend an initial fluid bolus of 30 mL/kg within 30 minutes of recognition of sepsis induced hypotension and titrating subsequent fluid therapy in accordance to fluid responsiveness to avoid excessive fluid loading. Dynamic variables such as passive straight leg raises or fluid challenges with systolic pressure, pulse pressure and stroke volume variations could be utilized for assessment of fluid responsiveness. A recent systematic review by Bednarczyk *et al.* showed that fluid resuscitation with dynamic assessment of fluid responsiveness was associated with reduction in mortality, intensive care unit (ICU) length of stay and mechanical ventilation (103). Vasopressors could be initiated early to an MAP of 65 mmHg for patients with septic shock in patients who remain persistently hypotensive and no longer fluid responsive (104). Early lactate clearance was associated with improved mortality and could be used to guide resuscitation (105,106).

The management of acute respiratory failure

Acute respiratory failure and acute respiratory distress syndrome (ARDS) are major complications and causes of mortality in severe CAP (107,108). Acute respiratory failure

or ARDS from severe CAP are major indications for prompt tracheal intubation and invasive mechanical ventilation. Early detection and stratification of respiratory failure and ARDS in pneumonia is based on the PaO_2/FiO_2 ratio (42). This requires serial sampling of arterial blood gas which is not convenient in most busy EDs. However, continuous, cheap, painless and non-invasive monitoring of oxygenation by pulse oximetry is routine practice in all acute medical settings. Thus, early and non-invasive detection and monitoring of ARDS can be perform efficiently by using the SpO_2/FiO_2 ratio (109-111). Because the imputation of PaO_2/FiO_2 from SpO_2/FiO_2 is non-linear, a decision needs to be made on pragmatic action points (112,113). In this regards an SpO_2/FiO_2 ratio of 235 which corresponds to an SpO_2/FiO_2 ratio of 200 would define the impending risk of ARDS (114). Alternatively, simple rule of thumb would be the need to increase the FiO_2 of 0.4 to achieve an SpO_2 of 100% (corresponding to an SpO_2/FiO_2 ratio of below 250). This could be translated into a simple practical rule of thumb that not patient with CAP should be admitted to a general medical ward on an FiO_2 of ≥0.4.

Some patients with respiratory failure from CAP may benefit from a trial of non-invasive ventilation (NIV) (115,116). But the clinical evidence for this practice, once acute exacerbations of chronic obstructive pulmonary disease are excluded, is not robust and thus, it is not recommended in the current official ERS/ATS clinical practice guidelines on NIV for acute respiratory failure (117). Similarly, in severe CAP, delivery of oxygen via high flow nasal cannulae (HFNC) may be better tolerated but gives no clear advantages to either O_2 or NIV (118-120). Moreover, just as in NIV, failure of HFNC delays tracheal intubation, is associated with sudden cardiovascular arrest and increased mortality (121). So, we suggest that in cases of uncertainty it might be safer to perform elective intubation and invasive ventilation rather than trials of either NIV or HFNC. In the latter situation, close monitoring and clear-cut time-lines and criteria for patient response versus failure should be agreed to, explicated and practiced consistently.

The role of corticosteroids

There is emerging evidence and growing consensus that treatment with systematic corticosteroids for relative adrenal failure may be indicated in patients with severe refractory septic shock (122). By contrast, despite some advocates for this treatment also in severe CAP, it is uncertain if patients with CAP who are not in shock will benefit (123-125). Corticosteroid treatment may suppress inflammatory cascades and promote transient improvements in clinical and radiological signs in patients who present with severe CAP and a strong inflammatory response (126). However, while this treatment may reduce mortality in severe CAP, it is associated with an increased risk for CAP-related rehospitalisation and hyperglycaemia (127,128). Thus, we recommend that systematic corticosteroids should be used only in patients with severe CAP who are also in refractory septic shock. Converse, in patients with severe CAP who are not also in septic shock, the benefits of steroid treatment is more equivocal and risk versus benefits of treatment should be evaluated carefully in every case (67,129).

On implementing and sustaining change

Because of its complexity and the lack of robust consensus on pivotal practice points, there is a paucity of randomized controlled trials on the management of CAP (130-132). There is also a lack of awareness among acute care physicians that severe CAP should be managed as a medical emergency with time sensitive action sequences. This is in sharp contrast with the situation in acute myocardial infarction which has similar mortality rates as (133,134). In myocardial infarction, the door-to balloon time is actively tracked, monitored, and reported as performance indicators against an established standard of practice with a view to further improvement (135). Cardiology and emergency medicine teams' co-ordinate and work keenly together to improve their performed on this quality indicator (136).

We recommend that severe CAP in the ED should be managed with an approach similar to that for severe sepsis and myocardial infarction (17,137). Timely execution of care bundles to identify severe CAP, administer initial antimicrobials, treat acute respiratory failure and septic shock are critical interventions (*Figure 1*) (17,29,132,138). Adept and detailed design of management programs and sustained efforts to ensure adherence to such interventions are required to translate knowledge into right, timely and effective actions at the beside (83). Monitoring appropriate metrics of health care team performance for objective, data-based, peer to peer feedback to improve adherence and accountability are key elements necessary for success and its maintenance over time (15,38). This process is similar to the implementation of severe sepsis bundles (104,137). In the case of severe CAP, in addition, we recommend

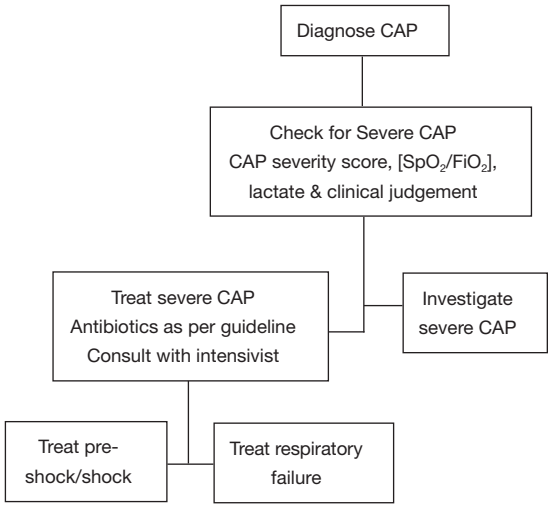

Figure 1 Management of severe CAP in the ED. CAP, community acquired pneumonia; SpO_2, oxygen saturation measured by pulse oximetry; FiO_2, fraction of inspired supplementary oxygen; ED, emergency department.

careful monitoring, review, audit and feedback of all delayed admissions to the ICU (28,139). This should also include patients who died from CAP after admission to the general wards from the ED who did not enter the ICU but also did not have any prior care limitation orders.

Limitations

The recommendations and suggestion in this review are not prescriptive since they are not based on a systematic, structured, formal, hierarchical meta-analysis of the clinical evidence. They are expedient solutions based on a heuristic interpretation of the best available evidence and our own experience in managing severe CAP over the past decade. At the very least it would serve as controversial and thus, trigger points for clinicians and researchers to re-examine our preconceptions and practices in this important area.

Conclusions

We have described the management of severe CAP in the ED following a qualitative, aggregative type review of the clinical evidence. We recommend the implementation of early triage processes, prompt antimicrobial treatment and resuscitation bundles for shock and respiratory failure in the management of severe CAP in the ED. We also made suggestions for sustaining and improving upon such an enterprise. We urge acute care physicians to not wait for further evidence to support optimal care of severe CAP but to take action now to save lives and avert complications and morbidities.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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