Antibacterial treatment of community-acquired pneumonia: the role of therapeutic agents other than the macrolides

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The optimal guidelines for the treatment of community-acquired pneumonia are not well established, and the relevant pathogen is often unknown. Initial choice of an antimicrobial agent should depend on the initial severity of the patient's illness, site of acquisition, age, coexisting illness and treatment setting. Few reliable studies have been performed to establish the supremacy of any antibiotic agent in this condition, either for ambulatory or hospital treatment.

Key words: community-acquired pneumonia, treatment guidelines, antibiotic therapy

Age-adjusted rates of pneumonia and influenza deaths continue to increase in the USA and presumably throughout the industrialized world [1]. Although 90% of deaths occur in patients over age 65 or in patients with underlying illness, pneumonia remains the sixth leading cause of death in the industrialized world. In one of very few population-based studies, Jokinen et al identified 545 individuals with pneumonia from a total population of 46,979 individuals living in four municipalities in the province of Kuopio, Finland [2]. The overall incidence of community-acquired pneumonia (CAP) per 1000 individuals was 11.6. Of these, 104 (19%) had predisposing significant underlying illnesses. Fifteen (4%) died and all but one of these had an underlying illness.

Patients presenting with CAP frequently have symptoms or signs which can be confused with other diagnoses. Radiologists disagree among themselves, with the rate of consensus for pneumonia of 80% at most [3]. As a result, the diagnosis of pneumonia requires a skilled physician interpreting the patient's history, and clinical and radiograph findings, while excluding other potential illnesses which could present as CAP.

ANTIMICROBIAL TREATMENT: SOME GENERAL PRINCIPLES

Infections are ideally treated by identifying a pathogen, selecting appropriate treatment, and administering it by the optimal route and for the appropriate duration to cure all patients. Although there have been various consensus statements developed for the treatment of

CAP by such groups as the American Thoracic Society [4], the Canadian Community Acquired Pneumonia Consensus Conference Group [5] and the British Thoracic Society [6], the 'optimal guidelines' for CAP are not well established. For most patients, we are guessing at the most likely pathogen, albeit with knowledge of the local epidemiologic patterns. The value of sputum cultures for patients treated outside hospital is debatable. In a recent review, Marrie attempted to get consensus through reviewing 37 textbooks [3]. Treatment choices and duration were extremely varied and not based on any rationale. Despite this, there is general agreement amongst infectious disease physicians that patients with CAP should be prescribed an antimicrobial agent. Consensus disappears when specific regimens are identified.

Treatment should be started promptly. Tang and McFarlane noted that the average interval between patients reaching hospital and receiving their first dose of antibiotics was 260 min [7]. This is not quality medicine. We would argue that most patients should receive their first dose within an average of 90 min, and no patients should go for longer than 120 min after reaching hospital before initial treatment. Concomitant underlying illness also should be managed urgently.

Previous reviews of physician choices suggest that there is wide variation, with tetracyclines, amoxicillin, sulfamethoxazole/trimethoprim, cephalosporins and fluoro-quinolones all being 'drugs of first choice' both for ambulatory patients and for patients requiring hospital admission [3]. These differences may also be observed in some of the consensus statements on the

treatment of CAP [5–7]. To our discredit as investigators, we have not carried out quality studies that enable eloquent argument for the choice of one antimicrobial agent in preference to another. Most therapeutic trials are carried out during the course of pharmaceutical sponsored treatment trials. In these studies patient entry is restricted, and is not usually representative of the wider population of patients ill with CAP. For instance, these trials usually exclude patients if no etiologic agent is identified. As has been pointed out in earlier papers in this Supplement, etiologic agents are usually only found in 50% or less of patients with CAP.

Initial antimicrobial choice should be based on four key stratification determinants [3]:

1. Initial severity of illness.
2. Site of acquisition (community or institution, e.g. nursing home).
3. Co-morbid illness/age over 65.
4. Treatment setting (home, nursing home or hospital).

Cost and physician and patient experience must also be considered.

AMBULATORY TREATMENT CHOICE FOR CAP

Although the macrolides are frequently recommended [4,5] to be the 'drug of choice' for outpatient treatment, studies to establish the correctness of this choice over other agents are lacking [3]. Tetracyclines are also identified by some recent authorities as being the optimal choice [8]. Again, definitive studies do not exist to substantiate this opinion. The emergence of *Streptococcus pneumoniae* resistant to penicillin and variably resistant to other therapeutic agents, including macrolides, tetracyclines and trimethoprim/sulfamethoxazole, further complicates the choice of treatment for patients who can be managed out of hospital. At present our choice, if a macrolide is not selected, is either trimethoprim/sulfamethoxazole or amoxicillin plus clavulanic acid for patients with CAP complicated by chronic airways disease. Amoxicillin or tetracycline are still excellent choices for patients with no underlying illness. Although a second-generation cephalosporin such as cefaclor is extensively prescribed, particularly for children, prospective studies have not proven it to be better than other regimens.

Frequently, physicians attempt to differentiate between typical and atypical presentations in order to select an antimicrobial agent. This has not proven to be useful in prospective critical studies [9]. In other words, CAP is the entity we are treating, not 'atypical pneumonia'.

Although the macrolides are effective against most pathogens, erythromycin and to a lesser extent other pathogens, erythromycin and to a lesser extent other macrolides are much less effective against *Haemophilus influenzae* in vitro.

HOSPITAL TREATMENT OF CAP

Less than 15% of patients with CAP require hospital admission [3]. Most physicians choose a β-lactam as initial treatment for patients requiring hospital admission, and cefuroxime seems to be the one preferred by many physicians in Canada [5]. There are no studies showing that it is superior to other regimens. A macrolide should be added for the 20% of patients in whom *Legionella*, *Mycoplasma pneumoniae* or *Chlamydia* are realistically possible pathogens. Again, studies have shown the fallacy of clinical diagnosis for these pathogens and we must accept overtreatment with the macrolides in many patients with pneumonia who require hospital admission. Therapeutic regimens must always include a macrolide if *Legionella* is a possible etiologic agent, particularly for critically ill patients.

As noted earlier, the duration of therapy is uncertain. We advise switching from a parenteral regimen to an oral regimen at 72 h, if no pathogens have been identified and the patient has responded. The patient can be discharged on oral therapy to complete a 10-day course. About 15% of patients admitted to hospital are the more seriously ill patients with CAP. Many of these will end up in intensive care units, where mortality remains high at 30–40% [5].

Physicians and their patients frequently have unrealistic expectations of rate of recovery. In particular, patients with co-morbid conditions such as heart failure, chronic airways disease or immobility may respond very slowly and take 2 to 6 weeks for radiologic resolution to occur [3]. Aggressive investigation or prolonged antibacterial treatment is usually not indicated unless there are clearly objective signs of therapeutic failure. Perhaps 5% of patients treated out of hospital will fail to respond as expected, with resolution of fever and clinical signs and symptoms within 3 to 5 days. Marrie has identified eight factors to consider routinely when patients with CAP fail to improve [3] (Table 1). This table should be learned by heart and reviewed prior to switching antibiotics (either to macrolides or to other antibiotics) when the treatment fails.

OTHER RELEVANT ISSUES

Several dilemmas in addition to antimicrobial choice are important determinants of care for patients with pneumonia.

First, could the pneumonia have been prevented with immunization with either influenza or pneumococcal vaccines? [10]. Too often we fail to consider this

Table 1 When patients with CAP fail to respond adequately to therapy

1. Is your diagnosis of CAP in error? Remember that all infiltrates are not pneumonia. Consider pulmonary infarction, vasculitis, neoplasm, heart failure, allergy.
2. Are you failing to treat the invasive pathogen(s)? At least 10% of CAP patients have *two or more* pathogens. Tuberculosis and fungi can mimic CAP.
3. Is the etiologic agent unexpectedly resistant to your regimen? This is an emerging serious problem with *S. pneumoniae* and *H. influenzae*.
4. Has a new or nosocomial infection occurred? This happens in 1–2% outside hospital and 4–10% in hospital.
5. Do you need to exclude bronchial obstruction?
6. Is there undrained pus or pleural fluid? Lung abscess or empyema?
7. Has metastatic infection spread elsewhere to the heart, bone, meninges?
8. Have you considered drug fever?
9. Are you or your patient unrealistic in your expectations?

Modified from Marrie [3].

during routine care of CAP. Even more surprising, following discharge from hospital with pneumonia patients are often not informed about the efficacy of both these vaccines. This must become part of our routine.

Second, the emergence of antimicrobial resistance worldwide among respiratory pathogens is causing consternation and revision of antimicrobial drug choices [11]. Although most evidence continues to suggest that *S. pneumoniae* CAP can be treated with β-lactam drugs despite resistance, failures will likely begin to occur with increasing frequency. Although there continue to be calls for 'more prudent use of antibacterial drugs' [12], the optimal strategy for prescribing these agents for pneumonia in order to forestall resistance is unknown. Studies to address this should be a priority, and include both macrolides and other effective therapeutic agents.

Third, the specific indications for the fluoro-quinolones remain uncertain. Although ofloxacin is being used widely for the treatment of respiratory infections, no studies have shown it to be superior to existing agents, and concerns remain about the development of resistance among Gram-positive cocci. Fluoroquinolones such as sparfloxacin may be superior to existing regimens but there are concerns about the safety profile of this class of drugs. Are the fluoro-quinolones as effective as the macrolides for *Legionella*, *Mycoplasma* and *Chlamydia*? Unfortunately, the studies to date are inadequate.

Fourth, despite the many studies and many therapeutic regimens available for CAP, we still do not have adequate internationally accepted guidelines for optimal management [4–6]. As our concerns increase

with limited funds for healthcare, we must improve our knowledge base and our strategies to convey to physicians and the wider public the most efficient use of healthcare money. Almost certainly this will not result in the selection of a specific group of antibacterial drugs. The Infectious Diseases Society of America has established guidelines for antibacterial trials [13] which should enable consensus to be developed and the formulation of specific guidelines. Until then we will have to rely on the inadequate data available and our own expertise as care providers. No one can currently be dogmatic or state with any authority the efficacy or effectiveness of a specific regimen.

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