Sensitive PCT Test for the Management of Antibiotic Therapy in Patients with Acute Respiratory Tract Infections

- To identify patients with clinically relevant respiratory tract infections
- To optimize antibiotic therapy of respiratory tract diseases
- To reduce the occurrence of bacterial resistance
Introduction

Acute respiratory tract infections are one of the most prevalent diseases in humans. When respiratory tract infections are suspected, antibiotics are too often and too readily prescribed. Antibiotics act against bacteria, however, approximately 80% of respiratory tract infections are caused by viruses – and antibiotics are ineffective against viral infections. This indiscriminate use of antibiotics leads to bacterial resistance and is also very costly. On the other hand, if antibiotics are given at an early stage and in a targeted manner – the general practice physician/outpatient physician is usually the first point of contact – this could reduce costs and prevent development of bacterial resistance.

A new, sensitive laboratory test enables an early detection of the bacterial etiology of respiratory tract infections – B·R·A·H·M·S PCT sensitive test provides diagnostic assurance for successful antibiotic therapy decisions.
Diagnostic Clarification of Bacterial Respiratory Tract Infections – Medical and Economic Relevance

It is commonly believed that general practice physicians/outpatient physicians prescribe too many antibiotics to patients with respiratory tract diseases. An urgent requirement for countering this problem is, besides continuing education and instruction of physicians, especially the **conclusive and early-stage differential-diagnostic clarification of the cause of infection**.

- Adults develop respiratory tract infections several times a year. In 2003 respiratory tract infections (RTIs) were responsible for 174,000 deaths in Europe and 3.8 million worldwide, accounting for 6% of the global and 1.3% of the European disease burden. As a result, the treatment of respiratory tract infections is the single most common reason for community-based antibiotic prescriptions in Europe (36%), even though in most cases the disease is virally induced. In the European Union (EU), RTIs cause 17% of deaths in men and 10% of deaths in women.

- The overall incidence for lower respiratory tract infections (LRTI) is 44 cases per 1,000 population per year (D, UK). Most incidences of RTI occur in the winter months.

- In the EU, chronic respiratory tract diseases (COPD, bronchitis, asthma, pneumonia...) cause 4.4% of deaths in men and 2.6% in women. Of these, chronic obstructive pulmonary diseases (COPD) are the most common. For country specific mortality rates, see Figure 1.

**Figure 1: Chronic lower respiratory diseases. Male/female ratio, age standardized mortality all ages (1994-96)**

![Figure 1: Chronic lower respiratory diseases. Male/female ratio, age standardized mortality all ages (1994-96)](image-url)
The WHO estimates that 600 million people worldwide are affected by COPD. It is the fourth most common cause of death and takes the live of more than 2.74 million people each year. For significance in larger countries, see Table 1.

Pneumonia is an infectious disease of the lower airways that often has a lethal outcome in industrial countries. In Europe, community-acquired pneumonia (CAP) is estimated to affect approximately 100 in 100,000 adults each year. In Germany alone, 800,000 people fall ill from CAP each year, with almost a third requiring hospitalization. This statistic significantly exceeds those of heart attacks or strokes.

Pneumonia is the leading cause of infection-related death in the elderly and remains one of the top five causes of mortality in persons 65 of age and older. In Europe, there are over 3 million cases of CAP annually with an estimated 2-3 million seen in the USA. In Europe, 15-51% of patients with CAP are hospitalized, generating considerably high, possibly unnecessary expenses. Improvement in the outpatient management of CAP could result in significant benefits for the patients.

CAP, with a death rate of 11%, is the most commonly reported infectious disease worldwide. For hospitalized patients, the death rate may even reach 20%. In Germany alone, the costs associated with CAP amount to more than € 500 million each year. The annual costs of treating CAP in the US are $ 12.2 billion.

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Table 1: Significance of COPD in larger countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Significance</th>
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<tr>
<td>Europe</td>
<td>In Western Europe, the prevalence is 4-10%. Estimates: Spain 1.8 million, UK 3 million, Germany 2.7 million, Italy 2.6 million, France 2.6 million.</td>
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<tr>
<td>USA</td>
<td>In 2001, approximately 13.3 million US citizens above age 18 suffered from COPD; 24 million revealed abnormal pulmonary function.</td>
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<td>Australia</td>
<td>Third leading cause of disease burden, and respiratory tract disease with the highest disease burden.</td>
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<td>New Zealand</td>
<td>Second leading cause of disease burden and respiratory tract disease (after stroke).</td>
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Antibiotic Prescriptions for Respiratory Tract Diseases

- According to estimates, more than 1 million tons of antibiotics have been released into the biosphere within the last 50 years. In Europe, roughly 13,000 tons of antibiotics were used in 1999. Of these, the largest share (65%) was for use in human medicine.³
- The largest volumes of antibiotic prescriptions for systemic use are prescribed in primary care, and respiratory tract infections are the most common indication. As much as 75% of antibiotics are prescribed for ARTI, despite their mainly viral origin.⁴
- Prescription of antibiotics in primary care in Europe varies greatly: the highest rate in France (32.2 DDD per 1,000 inhabitants daily), the lowest in the Netherlands (10.0 DDD per 1,000 inhabitants daily) (see Figure 2).¹³
- According to an estimate, 20-50% of all antibiotic prescriptions are prescribed unnecessarily.²,⁷
- It has been assumed for RTIs that 80% of all cases of acute bronchitis are not caused by bacteria but by viruses.²,⁷ Thus, antibiotic therapy is in many cases not indicated for this patient group.

Figure 2: Total outpatient antibiotic use in 26 European countries in 2002 ¹³

The overuse of antibiotics by the general practice physician/outpatient physician is easily comprehensible because, until now, no test has been available that differentiates between bacterial and viral infections. Now, the PCT test enables the identification of patients who require antibiotic therapy.
Procalcitonin – a Specific Marker of Bacterial Infection

Procalcitonin (PCT) is a highly sensitive and specific marker which can be detected in the blood stream in response to a bacterial infection. What is remarkable about PCT and distinguishes it from conventional infectious disease markers is that it permits the differential diagnosis between bacterial and viral infections.

During viral infection or nonbacterial inflammation, PCT concentration remains low whereas significantly elevated levels are found in bacterial infections. This remarkable and unique property of PCT aids the physician in making therapeutic decisions and also provides important clues as to whether antibiotic therapy for a respiratory tract infection is necessary and appropriate.

Based on test formats available since 1996, PCT has so far been determined primarily in critically ill patients admitted to medical and surgical intensive care units and has allowed early diagnosis and assessment of the course of severe bacterial infections and sepsis.

Now, PCT levels can also be determined at previously not measurable concentrations of less than 0.1 ng/mL. For these determinations, various measuring methods are available, including the fully automated B·R·A·H·M·S PCT sensitive KRYPTOR that delivers results in only 20 minutes with a minimum sample volume of 20 µL (see Figure 3).

Figure 3: Fully automated random access analyzer B·R·A·H·M·S KRYPTOR

Sensitive determination of PCT allows the assessment of bacterial respiratory tract infections. The concentration level of PCT provides information whether antibiotic therapy is required or symptomatic therapy will suffice. Therefore, general practice physicians/outpatient physicians can now access a reliable decision tool already used by clinicians in ICU therapy management.
Clinical Studies of PCT-Guided Antibiotic Therapy

1. The ProResp Study
Based on the sensitive PCT test described above, an interventional study was performed at the University Hospital of Basel, Switzerland, with the aim of using a diagnostic marker for guidance of antibiotic therapy in patients with infections of the lower respiratory tract. Due to the potentially far-reaching medical and therapeutical implications, the very favorable study results were published in February 2004, just a few days after submission, in a fast-track publication of the renowned medical journal *The Lancet*, and provoked considerable interest in the medical press as well as in the general public.

The study provided scientific evidence that antibiotic usage can be significantly reduced in patients with RTIs if therapy management is guided by PCT serum/plasma concentrations.

Nearly 50% of antibiotics normally prescribed for RTIs were saved without any negative impact on patient recovery. Particularly in patients with acute bronchitis or acute exacerbation of a chronic bronchitis, but also in asthmatic patients, the PCT test led to a significant decrease (approx. 70%) in antibiotic treatment.7

![Figure 4: Antibiotic prescriptions for patients with lower respiratory tract infections](Image)

**Figure 4: Antibiotic prescriptions for patients with lower respiratory tract infections**

2. The ProCAP Study
Following the ProResp study, the ProCAP study was performed. The focus of the study was the use of PCT as a decision criterion for determining the duration of antibiotic therapy in patients with community-acquired pneumonia (CAP). An initial preliminary evaluation of the results (200 patients) clearly shows that the duration of administration of antibiotics could be reduced by 50% without any impact on patient outcome.6

![Clinical Studies of PCT-Guided Antibiotic Therapy: Figure 4](Image)
3. The ProCOLD Study

The ProCOLD study was started together with the ProCAP study. Eighty patients with chronic RTIs were enrolled in the study. The aim of the study was to prove the safety and effectiveness of PCT-guided antibiotic therapy within this patient group. The results revealed that the PCT-guided approach led to a 42% decrease in antibiotic prescriptions for acute exacerbation of chronic bronchitis (AECB) without significant deviation in clinical outcome. Therefore, the conclusion that can be drawn is that PCT safely and significantly reduces antibiotic prescription for bacterial infections. The publication of these data is expected in 2006.

4. The PARTI Study

In 2004, the world’s largest intervention study of antibiotic usage (PARTI study) was started. The study enrolls 600 patients with RTIs and is performed exclusively in the general practice/outpatient environment. The hypothesis assumes that patients receiving PCT-guided therapy will receive fewer antibiotics. As target hypothesis, a 20% reduction of antibiotic usage and a 20% reduction in the duration of the administration of antibiotics was specified in the study design. The final results of this study will be available by the end of 2006.

Current studies show that by using a PCT-based algorithm, antibiotic usage can be cut by approx. 50% with similar clinical outcome. The PARTI study will provide the first-ever opportunity to evaluate such potential reductions in antibiotic usage for RTIs in the general practice/outpatient environment.
Present Problems Regarding Bacterial Resistance Are Closely Linked to Prescription Behavior

Antibiotic resistance is one of the most important problems worldwide facing public healthcare systems today. Besides the costs associated with unnecessary prescriptions, the negative side effect of bacterial resistance and its potentially life threatening effects are of critical importance.

Due to diagnostic uncertainty and the danger of overlooking a potentially dangerous bacterial infection, physicians prescribe antibiotics in a major part of LRTI cases, fully aware that a significant number of their patients probably have viral infections only. The result is a healthcare system burdened with considerable follow-up costs and a bacterial resistance problem that is having an increasingly adverse effect on infection control for severely ill patients.

Rates of antibiotic resistances remain low in Northern European countries, but the rates are reaching alarming levels in Southern and Central Europe. The degree of antibiotic resistance in strains of Staphylococcus Aureus (MRSA) is reaching frightening proportions. For Europe, rates of MRSA-related invasive infections vary between <1% to 50% (see Figure 6).9

In numerous studies, in part also performed in German maximum-care hospitals, it has been shown that MRSA infections are associated with considerable additional costs. The extra cost per MRSA patient in intensive care amounts to approx. €1,600 per day.22 The additional cost unit rate per patient and day charged by normal hospital units is still at approx. €400, from which on average an additional cost of approx. €9,300 per MRSA patient hospitalization is calculated.20

Figure 6: Staphylococcus Aureus: proportion of invasive isolates resistant to oxacillin (equivalents) in 20049
Statistical analyses of country-specific time trends showed that increases in MRSA proportions were significant in several countries. Figure 7 depicts significant time trends for MRSA proportions per country per year for 1999 through 2002.

Although costs vary greatly due to the different study design, setting, population, and year of publication, we have to take also into account the additional costs of:
- prolonged patient bed-rest periods,
- increased occurrence of postoperative complications,
- the use of, usually more expensive, reserve antibiotics,
- the increased diagnostic effort that is necessary to isolate individual patients or groups, in order to prevent the further spread of resistant bacteria,
- the microbiological monitoring of patients and personnel, and
- the absenteeism of employees.

One consequence of antibiotic resistance is open wound inflammation. It is the second most common type of nosocomial infections in Europe. These in turn are considered the fourth most common cause of death with estimated costs within the EU totaling approx. € 6.3 billion.

The occurrence of resistance can only be reduced if we succeed in reducing the frequency of antibiotic use. This can be reached by usage of antibiotics only in clinically confirmed cases. PCT as a specific marker for bacterial infections aids the physician in making informed clinical decisions for targeted and appropriate antibiotic therapy and reduces, besides unnecessary medication costs, the danger of generating antibiotic resistant germs.
References

15. librainitiative MEDIA FACT SHEET. Common Infectious Diseases. Community Acquired Pneumonia (CAP).

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