1. INTRODUCTION
1.1. CHRONIC OBSTRUCTIVE PULMONARY DISEASE
1.1.1. Epidemiology and definition
GOLD defines Chronic obstructive pulmonary disease (COPD) as “a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases” (5). It is a non-reversible and progressive disease. COPD is a common respiratory disease and is a major cause of death and disability worldwide (1,2). As reported by the World Health Organization (WHO), it affects more than 65 million people around the world, mainly (ex-)smokers older than 40 years (3). Ana S. M. Afonso et al. found
that the overall baseline prevalence of COPD in The Netherlands is 3.02% (4). Moreover, the prevalence is understated since COPD is underdiagnosed and thus also undertreated. Ageing of the world’s population leads to a higher prevalence. A prevalence that is still increasing and is expected to rise over the next 30 years (5). It is assumed that about 3 million people die annually because of COPD (5). By 2030, there may be over 4.5 million deaths each year (5). This upward trend is also due to continued exposure to risk factors and a lower death rate from other common causes (5). The prevalence is higher in people older than 40 because of structural changes in the airways and parenchyma due to ageing. The prevalence used to be greater among men than women, but it is almost equal now probably because women are catching up to men in smoking (5).

COPD was ranked as the fifth leading cause of disability-adjusted life years (DALYs) lost in 2013. The number of DALYs is a measure of the total burden which is caused by the disease. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) defined as “the sum of years lost because of premature mortality and years of life lived with disability, adjusted for the severity of disability” (5).

According to this data, it is not surprising that the morbidity, social and economic load are increasing. There is a clear link between the severity of the disease and the cost of care. Respiratory diseases are responsible for a cost of 380 billion euro each year in the European Union (EU) (6). Approximately half of these health care costs is attributable to smoking. The economic burden of COPD is estimated at 141.4 billion euro annually (6).

In contrast to COPD, the airflow limitation in asthma is usually fully reversible and not progressive. Asthma is defined by the Global Initiative for Asthma (GINA) as a “heterogeneous disease, usually characterized by chronic airway inflammation. It is defined by the history of respiratory symptoms such as wheeze, shortness of breath, chest tightness and cough that vary over time and in intensity, together with variable expiratory airflow limitation”. The most common form of asthma is the allergic form. It occurs at a younger age and is less related to smoking status. Symptoms often occur at night or in the early morning. The distinction between asthma and COPD is difficult to make. Significant overlap exists and is called asthma-COPD overlap syndrome (ACOS). GOLD and GINA describe ACOS as characterized by persistent airflow limitation with several features usually associated with asthma, such as stuffiness, wheezing, shortness of breath and nocturnal complaints, and several features usually associated with COPD, such as shortness of breath, cough, sputum production and fatigue. ACOS is therefore identified in clinical practice by the features that it shares with asthma and COPD, such as stuffiness, chronic cough and sputum production (5,7,8).

1.1.2. Symptoms and risk factors

COPD can be recognized by chronic and progressive dyspnea. Up to 30% of the patients also suffer from a cough with sputum production (5). The burden of the symptoms varies between days and may occur even before airflow limitation develops. And conversely, airflow limitation might be present in asymptomatic persons.

The first symptom of COPD, chronic cough, is not always recognized as a symptom but rather as an expected consequence of smoking. Rarely the airflow limitation develops without the presence of a cough. At first, the cough might be periodic, but after a time it may become a daily phenomenon. This cough may be associated with sputum production. If there is regular sputum production for three or more months in two consecutive years, it is defined as chronic bronchitis. COPD patients often complain of increased effort to breathe, chest heaviness, air hunger or gasping (5). Those symptoms are typical for dyspnea. Wheezing and chest heaviness varies during the day and from day to day, and even if absent a diagnosis of COPD can not be excluded. When fatigue, weight loss and anorexia are reported in patients with severe or very severe COPD, further investigation is recommended. Although these are common problems, they may be prognostic and may indicate the presence of other diseases, such as tuberculosis or lung cancer (5).

Sometimes respiratory symptoms go beyond normal day-to-day variations. These acute events are called exacerbations. They accelerate the decline in lung function and are assumed to be one of the most important causes of a reduced health status, morbidity, hospitalization and mortality (2).

Viral or bacterial infections and pollutants are the most important trigger factors to cause exacerbations (figure 1.1) (5,9,10). Viruses cause more severe exacerbations with a longer recovery time in comparison with bacteria explaining the importance of influenza vaccination in patients with COPD (10). The exact role of bacteria as a risk factor of COPD exacerbation remains unclear because colonization is also present in
patients with stable COPD. If purulent sputum is observed, it is more likely that positive bacterial cultures will be present, and treatment antibiotics might be initiated.

Figure 1.1: The most important trigger factors causing COPD exacerbations and the associated pathophysiological changes (10).

COPD is caused by complex interactions between risk factors, environmental exposures and a genetic predisposition. The major risk factor for developing COPD is exposure to tobacco smoke (5,11). Respiratory symptoms and lung function abnormalities may occur more often in cigarette smokers than non-smokers. They also have a faster decline in forced expiratory volume in one second (FEV1) and greater mortality rate. Even passive exposure to cigarette smoke may contribute to COPD (5). Yet fewer than 50% of the heavy smokers develop the disease (5). 25-45% of COPD patients have never smoked suggesting that other environmental risk factors are strongly associated with chronic airflow limitation (1). Indeed, occupational exposure and indoor and urban air pollution are known risk factors of airflow limitation, although their role is relatively small compared to the role of cigarette smoking, especially in adults. Air pollution does have a greater impact on lung maturation and development in children than in adults (5).

Other factors, some already present before birth, are important in the development of COPD. Those include maternal and paternal asthma, childhood smoking, maternal smoking and childhood respiratory infections. All of them are associated with poor lung growth, lung function and a reduced FEV1. Better monitoring of these factors could be important in the prevention of COPD (10,12).

There are genetic predisposing factors of COPD but these are not further discussed as this is not the scope of this thesis.

COPD patients often suffer from other comorbidities. The most common comorbidities are cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, anxiety and lung cancer (5). The Quality of Life (QoL) may decline more rapidly among those with multiple chronic conditions, and exacerbations may occur more often (13,14). Vice versa, more comorbidities are seen in patients who have frequent exacerbations.

1.1.3. Pathology, pathophysiology and pathogenesis

COPD is characterized by lung inflammation caused by noxious particles or gases. The response to these particles is more distinct in patients with COPD and leads to structural changes in the airways, lung parenchyma and pulmonary vasculature. One of these structural abnormalities in patients with COPD is emphysema. This is a destruction of the alveoli caused by inflammation. As a result of emphysema, the gas-exchanging surface decreases and an abnormal enlargement of airspaces arises. It is accompanied by a decrease in lung elastic recoil, which makes the airways susceptible to premature collapse during expiration (5). Another abnormality is chronic bronchitis that is characterized by cough or sputum production for at least three months in two consecutive years. It may lead to enlarged bronchial mucus glands, thicker walls and a narrowing of the lumen of small airways. Chronic bronchitis is a very useful clinically and epidemiologically term, but it only occurs in a minority of patients (5). This number is rising as the patients grow older and smoke more. These two comorbidities contribute to airflow limitation but do not necessarily occur together. The airway obstruction results in hyperinflation which reduces the inspiratory capacity. Increased dyspnea and limitation of exercise are the results from an increased functional residual capacity. The two processes are shown in figure 1.2.

Figure 1.2: Chronic inflammation in patients with COPD may cause chronic bronchitis and/or emphysema (15).

The pathogenic mechanisms of COPD are strongly interrelated. As the lung inflammation is still present upon smoking cessation, autonomous mechanisms must be involved. Exposure to cigarette smoke activates several pattern recognition receptors (PRR) expressed by various cells in the airway. Damage-associated molecular patterns (DAMP) will be released and can cause injury to epithelial cells (9,16). Innate immune cells, such as macrophages, neutrophils, eosinophils, mast cells, natural killer cells and dendritic cells, recognize those danger signals and are activated. Activated macrophages release inflammatory mediators and chemokines, which recruits other immune cells. Macrophages also produce reactive oxygen species and release proteolytic enzymes, such as neutrophil elastase. Due to the higher concentration of proteinases, there is a disruption of the balance between cell death and replenishment of elastin. If this connective tissue component of the lung parenchyma is destroyed, emphysema will occur (9,17,18). Neutrophils produce neutrophil elastase and that
contributes to alveolar destruction and stimulates the mucus secretion from gland cells. An excessive mucus production and impaired clearance can contribute to airway obstruction (16). Bacterial infections can arise when neutrophils are deficient in their antimicrobial activity (9,17,18).

In patients with COPD, increased amounts of cytotoxic T lymphocytes are observed in the induced sputum, compared with healthy smokers. Those lymphocytes release cell-killing enzymes, such as perforin and granzyme B. Higher amounts of those enzymes correlate with a more severe disease pattern. Perforin and granzyme B cause damage which contributes to a chronic inflammation (9).

1.1.4. Diagnosis
The gold standard for the diagnosis of COPD is spirometry. It should be obtained in any patient with symptoms as dyspnea, chronic cough or sputum production and/or a history of risk factors. Spirometry is a reproducible and noninvasive test. Though it has a good sensitivity, the specificity is weak. During the test, the patient needs to blow as hard as he/she can into a tube connected to the spirometer. After this initial step, the patient receives a bronchodilator and the test is repeated after 30 minutes. Spirometry gives an idea about the airflow limitation by measuring the forced expiratory volume in one second (FEV1) and the forced vital capacity (FVC), and calculating the ratio of these two measurements (FEV1/FVC). FEV1 is the maximum volume of air that can be forcibly exhaled in one second after complete inspiration. FVC is the maximum total volume of air that can be forcibly exhaled. Patients with COPD show a decrease in both FEV1 as FVC, as illustrated in figure 1.3 (5).

Figure 1.3: The differences in forced expiratory volume in one second (FEV1), forced vital capacity (FVC) and FEV1/FVC between the normal trace of a patient and a patient with chronic obstructive pulmonary disease (COPD) (19).

A post-bronchodilator ratio of FEV1/FVC lower than 0.70 confirms the presence of airflow limitation. A classification of the severity of COPD is based on post-bronchodilator FEV1 values compared to a predicted value for a normal subject of the same age, sex, height and ethnical origin published by the Global Lung Initiative (GLI) (20). COPD severity is classified into 4 categories: mild, moderate, severe and very severe (5,11). There are questionnaires available for people with COPD. For instance, the COPD assessment test (CAT) measures the impact of COPD on a person’s life, and how this changes over time. Second, the COPD control questionnaire (CCQ) is designed to measure the health status of patients with COPD. Third, St. George’s respiratory questionnaire (SGRQ) also measures the health status and QoL in patients with diseases of airway obstruction. Last, the modified medical research council (mMRC) scale is used in the assessment of dyspnea in chronic respiratory diseases. Categorization of the patients is mostly done by SGRQ and mMRC scale. This leads to four subgroups: A, B, C and D, that can be seen in figure 1.4 (5,11,21).

Figure 1.4: GOLD classification of severity of airflow limitation in COPD (5).

It should be said that there will be more diagnoses of COPD when the FEV1/FVC ratio is used, than when the lower limit of normal (LLN) is used for diagnosis. Because the FEV1/FVC ratio decreases with age, potential overdiagnosis occurs in elderly. On the other side, COPD is often underdiagnosed in 30 to 40-year-olds (figure 1.5) (22). Some recommend the use of the fifth percentile LLN over the FEV1/FVC ratio, but GOLD favors the use of the fixed ratio over LLN because misdiagnosis and over-treatment rarely occur when using the fixed ratio as a diagnostic criterion. And patients who have a ratio lower than 0.7, but a value higher than the LLN already have a greater mortality (5).

Figure 1.5: Effect of age on FEV1/FVC ratio and definition of chronic obstructive pulmonary disease (22). Other investigations can be conducted additionally to spirometry. A chest X-ray can provide more certainty in excluding alternative diagnoses. Computed tomography (CT) of the chest can be useful in patients meeting the criteria for lung cancer risk assessment or patients being evaluated for lung transplantation. Pulse oximetry can be used by patients in need for oxygen therapy to measure the arterial oxygen saturation. If more precise measurement of blood gases and pH is needed, assessment of an arterial blood sample adds valuable information (5). Walking tests are a powerful indicator of the health status deterioration and are a good predictor of survival. Both the paced shuttle walk test and the 6-minute walk test can be used. The BODE (body mass index, the degree of airflow obstruction and dyspnea, and exercise capacity) method combines all these factors and composes a score that predicts the prognosis better than each test separately (5).

1.1.5. Treatment
COPD is treatable, but not curable, because there is no medication that slows down or reverses the accelerated decline in lung function. The pharmacologic therapy is based on controlling COPD symptoms, reducing the occurrence and severity of exacerbations, improving exercise tolerance and health status. Smoking cessation is the only intervention that can slow down the disease progression (23). First, smoking cessation should be encouraged in all patients. Influenza vaccine and pneumococcal vaccine are recommended for all patients because they seriously reduce the exacerbation risk and death. The vaccines are more effective if they contain either killed or live inactivated viruses (5).

Medical treatment of COPD is added step by step (table 1.1). In principal treatment consists of maintenance therapy and reliever therapy. Reliever therapy can be used during an acute exacerbation and consists of short-acting beta 2 agonists (SABA) or short-acting muscarinic antagonists (SAMA). The use of SABA and SAMA should be minimized. Maintenance therapy exists of long-acting beta 2 agonists (LABA) or long-acting muscarinic antagonists (LAMA) eventually in combination with inhaled corticosteroids (ICS), theophylline or inhibitors of phosphodiesterase (PDE) type 4. Combining these medications can increase the degree of bronchodilation with lower side effects due to the lower doses. Aerosol administration is preferred over oral therapy because of more targeted therapy and thus less unwanted side effects and faster onset of action (24).

Table 1.1: Different classes of respiratory drugs used in patients with COPD and their corresponding anatomical therapeutic chemical (ATC) code.

<table>
<thead>
<tr>
<th>ATC Code</th>
<th>Active component</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAMA</td>
<td>R03BB04</td>
</tr>
<tr>
<td></td>
<td>Tiotropium bromide</td>
</tr>
<tr>
<td></td>
<td>R03BB05</td>
</tr>
<tr>
<td></td>
<td>Aclidinium bromide</td>
</tr>
<tr>
<td></td>
<td>R03BB06</td>
</tr>
<tr>
<td></td>
<td>Glycopyrronium bromide</td>
</tr>
<tr>
<td>LABA</td>
<td>R03AC12</td>
</tr>
<tr>
<td></td>
<td>Salmeterol</td>
</tr>
<tr>
<td></td>
<td>R03AC13</td>
</tr>
<tr>
<td></td>
<td>Formoterol</td>
</tr>
<tr>
<td></td>
<td>R03AC18</td>
</tr>
<tr>
<td></td>
<td>Indacaterol</td>
</tr>
<tr>
<td></td>
<td>R03AC19</td>
</tr>
<tr>
<td></td>
<td>Olodaterol</td>
</tr>
<tr>
<td>LABA + LAMA</td>
<td>R03AL03</td>
</tr>
<tr>
<td></td>
<td>Vilanterol and umeclidinium bromide</td>
</tr>
<tr>
<td></td>
<td>R03AL05</td>
</tr>
<tr>
<td></td>
<td>Formoterol and aclidinium bromide</td>
</tr>
<tr>
<td>ICS</td>
<td>R03BA01</td>
</tr>
<tr>
<td></td>
<td>Beclomethasone</td>
</tr>
<tr>
<td></td>
<td>R03BA02</td>
</tr>
<tr>
<td></td>
<td>Budesonide</td>
</tr>
<tr>
<td></td>
<td>R03BA05</td>
</tr>
<tr>
<td></td>
<td>Fluticasone</td>
</tr>
<tr>
<td></td>
<td>R03BA08</td>
</tr>
<tr>
<td></td>
<td>Ciclesonide</td>
</tr>
<tr>
<td>LABA + ICS</td>
<td>R03AK06</td>
</tr>
<tr>
<td></td>
<td>Salmeterol and fluticasone</td>
</tr>
</tbody>
</table>
Formoterol and budesonide
Formoterol and beclomethasone
Vilanterol and fluticasone furoate
Formoterol and fluticasone

Xanthines
Theophylline
Oral phosphodiesterase 4 inhibitors
Roflumilast

Oral β2 agonists
Salbutamol
SAMA
Ipratropium bromide
SABA
Terbutaline
SABA + SAMA

Fenoterol and ipratropium bromide
Salbutamol and ipratropium bromide

β2 agonists stimulate the β2 adrenergic receptors on smooth muscle cells, resulting in more cyclic adenosine monophosphate (cAMP) production that antagonizes bronchoconstriction. Adverse effects of SABA (salbutamol, terbutaline) and LABA (formoterol, salmeterol, indacaterol, olodaterol) are palpitations, trembling hands and headaches. Most side effects are observed during the first weeks of treatment and decline or disappear thereafter. More severe side effects, such as ischaemia, arrhythmias and QT prolongation, are rare (25).

Muscarinic antagonists, also known as anticholinergics, inhibit the muscarinic M3 receptors and prevent acetylcholine to bind muscarinic receptors resulting in bronchodilation. The long-acting anticholinergics (tiotropium bromide, aclidinium bromide, glycopyrronium bromide) have a more prolonged binding than the short-acting muscarinic antagonists (ipratropium), so bronchodilating effects last longer. A side effect that generally occurs three to five weeks after the start of the medication is a dry mouth, but usually disappears after some time. Other side effects are nausea, constipation and urinary retentions. Cardiovascular adverse events such as cardiac arrhythmias also have been associated with muscarinic antagonists in observational studies and clinical trials (25).

Inhaled corticosteroids are glucocorticoids that bind to intracellular glucocorticoid receptors and reduce the lung inflammation by decreasing the swelling and mucus production. They inhibit the transcription of steroid-sensitive target genes with lower production of cytokines as result. Monotherapy with ICS is not recommended in patients with COPD because the risks are greater than the benefits. (Chronic) use of ICS increases the risk of important adverse events such as pneumonia and fractures (25). Milder adverse events are a hoarse voice or an oral candidiasis in the mouth and throat. This arises because a portion of the drug remains behind in the mouth and throat. Correct use of the inhalator can prevent this. Rinsing the mouth with water and spitting it out after puffing may also help, just as brushing the teeth after inhalation.
Theophylline is a xanthine derivative and is one of the older drugs used for the treatment of COPD. It inhibits non-specific phosphodiesterase enzyme subsets with a reduced degradation of cAMP and cGMP (cyclic guanine monophosphate) as result. It also antagonizes the adenosine receptors, which has a bronchodilating effect. Theophylline is influenced by cytochrome P450 (CYP450) metabolism and has a small therapeutic ratio. The metabolic clearance of the drug decreases with age and increases by cigarette smoke due to the changes in CYP1A2 concentration. Smoking cessation can thus cause higher plasma levels of theophylline, so toxic effects are often observed when a patient quits smoking while on treatment. Theophylline also interacts with other drugs, so the use of theophylline is limited in patients with comorbidities (26).

PDE 4 inhibitors (roflumilast) inhibit phosphodiesterase 4 enzymes, which break down cAMP. So, a higher intracellular concentration of cAMP suppresses immune and inflammatory cell activity and relaxes airway smooth muscle. Nausea, diarrhea and abdominal pain are the main adverse effects (26). An advantage of PDE 4 is that it does not share the limitations of theophylline (27).

Figure 1.6: The step-up treatment scheme of COPD (28).

Figure 1.6 describes the treatment step up in patients with COPD. In patients with mild COPD, reduction of risk factors and use of short-acting bronchodilators might be sufficient. If patients remain symptomatic, treatment with LABA or LAMA is added, eventually in combination if symptoms remain. A fixed combination of these two is associated with a lower risk of side effects compared to an increased dose of a single component (25). In patients with severe COPD and repeated COPD exacerbations, treatment with ICS will be added. In patients with very severe COPD and respiratory failure, chronic use of oxygen is initiated. In principal, use of SABA or SAMA is only indicated during COPD exacerbation (either mild, moderate or severe). Exacerbations are called mild if a higher dose of regular medication is sufficient, moderate if corticosteroids and/or antibiotics are required, and severe if hospitalization is needed (29). An initial exacerbation increases the chance to a subsequent event (29).

1.1.6. Treatment failure

It is important to assure that the medication is taken correctly and that the patient is compliant before treatment step up (figure 1.6). A significant relationship exists between poor inhaler use and bad symptom control. More than two-thirds of the patients do not use the inhaler device correctly. There are three types of inhaler devices. Pressurized metered dose inhalers (pMDI) which deliver medication by using a propellant spray. They require a good hand-breath coordination. If this coordination is an issue, they can be used with a spacer but a part of the drug then sticks to the sides. Dry powder inhalers (DPI) contain micronized powder which de-agglomerates with adequate inhalation. They are often used in patients with bad hand-breath coordination, but require a high inspiratory flow and are difficult to use in patients with severe/very severe COPD. Mistakes that are frequently made are no shaking before use, the lack of coordination, the lack of breath-holding after inspiration, inhaling through the nose and interruption of inspiration (30). Pharmacists are crucial for an optimal inhalation of COPD drugs through the teach back principle and regularly verify the patients’ proficiency (29,31). The third type inhaler is the soft mist inhaler. It can be used by patients who have a low inspiratory flow or when the patients do not cooperate (children and elderly). But this device is expensive, must always be supplied with power and loses an important part of the drug due to expiration. Another possibility of treatment failure is a lack of adherence. Adherence refers to the extent in which the intake of the medication matches the recommendations of the prescriber. In chronic diseases such as COPD, poor adherence is a frequent phenomenon, especially in the elderly and in patients with comorbidities like depression (32). Other common reasons for non-adherence include income, mobility, knowledge and beliefs. Adherence is extremely important, otherwise, the medication will not be optimally effective. Only if the medication is used properly, it will lead to better healthcare outcomes, improve survival and reduce healthcare utilization (33). Non-adherence is one of the most important causes of the rising rates of health care costs, hospitalization and death (34). One should differentiate between intentional and unintentional non-adherence. In unintentional non-adherence, the patient wants to take the medication but is not able to. This can be due to various reasons such as cognitive impairments, misunderstanding of treatment instructions, financial constraints or inability to use the drugs/device properly, but the most common reason for non-intentional non-adherence is complex medication regimes and polypharmacy (33). Intentional non-adherence refers to patients who can take the medication, but do not want to. Reasons can be because they are asymptomatic, and do not recognize benefits of taking the medication or because of fear of adverse drug
reactions. S. Mueller et al. found that up to two-thirds of patients fail to continue the treatment after 12 months (34).

One measure to calculate adherence is the modified medication possession ratio (mMPR). The mMPR is the ratio of the sum of the number of days’ supply received divided by the time interval between the last and first prescription plus the duration of the last prescription (figure 1.7). The higher the adherence is, the higher the mMPR will be. A patient is considered adherent if the mMPR is higher than 80% (35).

Figure 1.7: Adherence calculation example of the modified medication possession ratio (mMPR) (36).

Another measure is the proportion of days covered (PDC). PDC is the ratio of the sum of the number of days covered by prescription divided by the time interval between the end of the observation period and the first prescription. Overlapping of prescriptions is not possible, because overlapping arrays are moved forward to the first day that the patient will run out of medication. Therefore, it is impossible to calculate a PDC greater than 100%. For multiple drugs, it does not average for the individual drugs but considers the days within a particular period when a patient is covered for all drugs. A patient is considered as adherent if the PDC is higher than 80%. PDC is more conservative than mMPR as it assumes the need for chronic therapy and thus uses the entire follow-up period (37).

Figure 1.8: Adherence calculation example of proportion of days covered for concomitant therapy (38).

The controller/total ratio (CTR) is a measure which is often used in epidemiological research to investigate whether the disease of a patient is under control. The term control is defined by the absence of limitations in activities, the absence of exacerbations, the absence of nocturnal symptoms, a minimum or no diurnal symptoms or no need for rescue medication. The denominator of the CTR consists of all drugs prescribed to the patient thus the sum of the maintenance therapy plus the rescue therapy. The nominator only consists of maintenance (controller) medication. In principle, in patients with controlled COPD, use of rescue medication should be low and the ratio should ideally be one. Some studies have shown that patients with a low controller/total ratio are at risk of COPD exacerbations, so it can be used as a quality-of-care measurement to help preventing exacerbations by identifying patients with a higher risk (35). Patients with a ratio higher of 0,5 are classified as high-ratio patients, and those with a ratio lower of 0,5 are classified as low-ratio patients.

About Essay Sauce

EssaySauce.com is a completely free resource to help students research their academic work and learn from great essays!

View all posts by Essay Sauce

...(download the rest of the essay above)
Please note that the above text is only a preview of this essay. The full essay has 4256 words and can be downloaded free in PDF format, using the link above.

Latest reviews:

- Miscellaneous essays
- Contract law and duress
- Push over analysis of multi storied RCC buildings

Search for student essays:

Search ...

About EssaySauce, the student essay site:

EssaySauce.com is a free resource for students, providing thousands of example essays to help them complete their college and university coursework. Students can use our free essays as examples to write their own.
Latest student essays:

Harnessing energy through knowledge – business development strategy of e-commerce companies
Minimizing of power losses for distribution system
Translating the Biggles Stories for Czech Readers: A Case of Moderate Transposition
Questioning is a Useful Form of AfL
Enhancing literacy
Cadburys
Advancements in Procurement Practices and Supply-Chain Management...
LITERARY REVIEW – fashion industry
Chlorpyrifos
Get out of my space – business idea

Student essay categories:

Accounting essays
Architecture essays
Business essays
Economics essays
Education essays
Engineering essays
English language essays
English literature essays
Environmental studies essays
Finance essays
Health essays
History essays
Information technology essays
International Relations
Law essays
Literature essays
Management essays
Marketing essays
Miscellaneous essays
Music Essays
Photography and arts essays
Politics essays
Project management
Psychology essays
Religious studies and Theology essays
Science essays
Sociology essays
Zoology essays

Average review:

Overall rating: 0 out of 5 based on 0 reviews.

Q: Is EssaySauce.com free?

Yes! EssaySauce.com is a completely free resource for students. You can view our terms of use here.

Why use Essay Sauce?

The brightest students know that the best way to learn is by example! EssaySauce.com has thousands of
great essay examples for students to use as inspiration when writing their own essays.

**Is Essay Sauce completely free?**

Yes! EssaySauce.com is a completely free resource for students. You can view our terms of use here.

**Info:**

- About
- Content policy
- Essay removal request
- Privacy
- Terms of use