Overlap Syndrome

By John R. Goodman BS RRT

The term “Overlap Syndrome” is one that is relatively new to medicine. As one might expect, the term refers to diseases that overlap one another so that the combined effect of multiple diseases or conditions are worse than either one alone. There are many examples of this in medicine especially well known in the group of known as Auto-immune diseases such as Arthritis, Lupus, Sjogren’s syndrome, Reynaud’s disease etc.

But there are two diseases that are very prevalent in our general patient population that might be easy to overlook. I am speaking of Chronic Obstructive Pulmonary Disease (COPD) and Obstructive Sleep Apnea (OSA). Let’s look at these one at a time beginning with COPD. Did you know that in 2008 COPD became the third leading cause of death in the United States? This was in a report released by the Centers for Disease Control (CDC), and is doubly troubling because COPD has not seen the same decrease in mortality that has been seen in heart disease, cancer or stroke. In fact there is another term being introduced to our respiratory “alphabet soup.” It is CLRD or Chronic Lower Respiratory Diseases. Basically these include emphysema, chronic bronchitis, and bronchiectasis. Approximately 24,000,000 Americans are affected by CLRD, but only 12,000,000 are currently diagnosed. The direct cost of CLRD in the United States is estimated at more than 32 billion dollars per year, and accounts for over 119,000 deaths annually.

COPD has been recognized for more than 300 years. In fact it was the autopsy of a famous English essayist, Dr. Samuel Johnson who had a history of being troubled for many years with a sense of dyspnea, and peripheral edema. His autopsy was performed in December of 1784, by John Wilson who observed that when he opened the chest cavity, “the lungs did not collapse as they usually do, but remained distended or hyperinflated.”

Dr. Samuel Johnson doesn’t look like he feels too well in this painting.
A few years later the brilliant French physician Rene Laennec described COPD with the use of his ground breaking invention…the stethoscope in 1821. Laennec was the first to identify inflammation as part of COPD. Also, the blue color we now know as cyanosis in advanced cases of COPD. Laennec also described the enlargement of the right side of the heart. With the invention of the first true spirometer by Hutchinson in 1846, COPD could be much more accurately diagnosed based on the volume of air contained in the lungs, and later, the flow rates at which that air could be expelled. Until Laennec’s stethoscope, physicians simply placed their ear against the chest of the patient to listen to breath sounds. Laennec’s stethoscope spared the physician the embarrassment of placing his ear directly on the chest of his female patients. Ironically, Laennec died of tuberculosis at the age of 45, just a few years after the invention that would bring him fame.

COPD by any of its associated names is definitely not a new disease. It had been largely ignored and it existed way before cigarettes were in widespread use. Let’s contrast COPD that we have known about for hundreds of years with OSA. The clinical features of OSA were first described in the medical literature in the 1960’s. But, historically, if not medically, Charles Dickens (in “The Posthumous Papers of the Pickwick Club”) describes Joe the fat boy as “the obese young man that was sleepy and snoring, he was always asleep, goes on errands fast asleep, and snores as he waits at the table.” For many years this was known as “Pickwickian Syndrome.” Today we recognize obesity, snoring, and daytime sleepiness as hallmarks of the condition known as OSA.

In 1976 Christian Guilleminault coined the term Obstructive Sleep Apnea.
Although OSA was thought to be a condition that developed only in obese individuals we now know this is certainly not always the case. In fact, one school of thought advances the theory that OSA may also be related to changes in the structure of our modern jaw in response to major changes in our diet (more refined and mushy foods), as well as the introduction of bottle-feeding. Whatever the cause, according to the National Sleep Association, 18 million people suffer from sleep apnea in the United States alone. To complicate things a little bit more, sleep apnea can be further split into obstructive sleep apnea/hypopnea (OSAH) disorder, central sleep apnea (CSA), and even mixed sleep disordered breathing. We will concentrate solely on OSAHS in this article, and abbreviate it as OSA. Sleep apnea is not a condition to be taken lightly. Around 38,000 people die every year from complications of OSA. It is estimated that 75% of people with OSA remain undiagnosed.

Did you know there is even a medical condition called Congenital Central Hypoventilation Syndrome? This is a pretty rare respiratory disorder that can be fatal if not treated. Persons with this syndrome classically stop breathing when they go to sleep. It may be present at birth or it may be due to some severe neurological trauma or damage to the brainstem. It is so rare; it is only seen in about 1 in every 200,000 live births. At any one time there are probably fewer than 300 known cases worldwide. It is also known by another name…”Ondines Curse.” With a name like that there must be a story right? And so there is.

Ondine was a beautiful water nymph and a true free spirit. Like all nymphs and mermaids, she was leery of men, as she knew if she were to ever fall in love with a mortal man and bear his child, she would lose her eternal youthfulness and everlasting life. By chance a handsome young man named Palemon was taking daily walks in the forest and he glimpsed Ondine and was taken by her incredible beauty. Eventually they talked and fell in love. He broke his engagement to a young noblewoman named Berta and with time and patience he convinced Ondine to marry him. Palemon vowed on their wedding day that “My every waking breath shall be my pledge of love and faithfulness to you.” But as in so many myths and fairy tales it was not to be.

The following year Ondine gave birth to their first child and from that moment on her incredible beauty began to fade, her body age, and Palemon’s eye began to wander to the younger woman to be found at his court. One day while walking in her gardens Ondine heard noises coming from the stable, and upon entering, she found Palemon with his arms wrapped around his former fiancée Berta. Ondine was furious with her husband and with what was left of her powers she uttered her
curse “You pledged faithfulness to me with your every waking breath, and I accepted that pledge. So be it. For as long as you are awake, you shall breath. But should you ever fall asleep, that breath will desert you.” And so it was Palemon would never sleep again.

Don’t mess with Ondine!

So to review, we have described a little bit about the history and background of two very different sets of clinical entities. Even by the lowest estimates, there are millions of people who have been diagnosed with either COPD or OSA. There are millions yet to be diagnosed. It shouldn’t be too much of a stretch to see how these two conditions could easily (by chance alone) “overlap.” And indeed they do.

Dr. Flenley

The Overlap Syndrome was first described by David Flenley in 1985. Flenley was among the first to speculate that the overlapping of COPD and OSA would have greater deleterious effect on the patient than either condition alone. In medicine we call this an “additive” effect. As if $1 + 1 = 3$. While there are reasonable estimates of the prevalence of OSA and COPD alone, estimates of prevalence of Overlap Syndrome are not so easy to get. Chance alone suggests that a patient with one disorder has a 10% chance of having the other. A handful of studies have shown the percentage of patients who may overlap to be between 20 and 40 percent. Even if we go with the 10% figure, it represents a huge number of potential overlap patients given the millions of patients already and yet to be diagnosed with both COPD and OSA.
A regular reader of our articles of the month might begin to put the full picture together in the following manner. What is the most common denominator of both conditions? The answer of course is hypoxia. The COPD patient is hypoxic most or all of the time, and the OSA patient is hypoxic during his/her apneic episodes while they are sleeping. Additionally, the COPD patient further desaturates at night due primarily to hypoventilation (usually breathing in a smaller volume with each breath). In fact, patients with Overlap Syndrome have *30 times more episodes of nocturnal desaturation* (saturations less than 85%) than either COPD or OSA alone. The net-net of all this is a double whammy effect on the heart. More specifically the right side of the heart and development of Pulmonary Arterial Hypertension or PAH. (You might want to go back and review the article I wrote on PAH). Early on when OSA was first being described, the transient drops in oxygen saturation were not thought to be all that harmful to the heart. We now know that this is of course not true. In fact, nocturnal desaturation is a well known marker of increased mortality, and may even explain why COPD patients are reported to die more frequently during the night than might otherwise be expected. We do know that 10% of OSA patients have evidence of COPD and right heart failure.

There are other clinical consequences of Overlap Syndrome such as significantly worse quality of life, but it is the effect on the heart that is of greatest concern due to the increased mortality associated with PAH. Although the exact mechanism(s) for the increased risk of dying are not exactly known, it is reasonable to assume that the more prolonged hypoxic periods contribute to the finding. There is also some preliminary evidence that OSA may contribute to an increase in the frequency of COPD exacerbations.

And just for the record, patients with Idiopathic Pulmonary Fibrosis (IPF) may also be victims of Overlap Syndrome. A well done study at Vanderbilt University of 50 patients who were known to have IPF, found 88% of those patients also had documented OSA.
You would think Overlap Syndrome would be easy to diagnose. Actually it *is* easy to diagnose IF the attending physician has the awareness that Overlap Syndrome might be a possibility. Obviously awareness should be triggered when taking the patient’s history, and evidence of either COPD or OSA is determined. It is not unusual for patients with severe COPD to tell their physicians that they sleep poorly, or have other signs of poor sleep such as day time sleepiness. These patients should probably have a full sleep study to see if indeed they also have OSA. Patients with mild to moderate COPD should at least have a nocturnal oximetry study, especially if there is already evidence of pulmonary hypertension. Conversely, OSA patients who have arterial blood gases that reflect increased daytime carbon dioxide should probably undergo investigation for COPD.

Diagnosing Overlap Syndrome can provide helpful prognostic information which may help direct treatment for other underlying conditions. COPD patients who have sleep studies performed should make sure the sleep technologist knows they have COPD as it may influence the CPAP titration. Lastly, diagnosing Overlap Syndrome may well help the physician with the diagnosis and treatment of PAH utilizing echocardiography or even right heart catheterization.

It should be fairly clear by now that the treatment of Overlap Syndrome includes the treatment of both conditions as if they alone existed. The primary emphasis as you might expect is to maintain normal oxygen saturation levels while awake and
certainly during sleep. We know from the original NOTT study that the group of patients receiving continuous oxygen therapy had a much greater survival percentage than the patients who received oxygen only at night.

Anything that improves oxygenation, especially nocturnal oxygenation should be of benefit. Inhaled bronchodilators and the use of oral and inhaled steroids should help improve oxygen saturation, and might even allow lower CPAP pressures in patients with OSA. If oxygen is the essential “drug” to cover both COPD and OSA, then CPAP is the current treatment of choice to treat patients with OSA. Some of you may be aware of another form of positive pressure therapy called Non-Invasive Ventilation or NIV. Basically a variation of CPAP, with a pressure generating machine that aids or assists patients breathing especially useful during the night. Several studies have proven that NIV actually does improve mortality rates for patients with Overlap Syndrome…but this has to be tempered by the fact that the same patients reported a decreased quality of life. Whether NIV works better than CPAP has yet to be determined, but is an area for future study.

NIV needs further…… study to see if it is the…… treatment of choice for Overlap Syndrome

COPD has been identified and studied now for over 300 years. OSA and related disorders of sleep have been studied intensively since the mid 1960’s. The “overlapping” of these two pulmonary conditions was only first described in 1985. It is safe to say that if current estimates on the number of patients with COPD (24,000,000) and OSA (18,000,000) are reasonably accurate, and we use the 10% figure who by chance alone are “over lappers” than there are hundreds of thousands of patients in the general population yet to be diagnosed and treated for Overlap Syndrome. Here’s a question I’ll leave you with. Whether you have been diagnosed with COPD, ILD, or any other respiratory disease that features chronic hypoxia…has your family practice physician, cardiologist, or pulmonologist talked to you about Overlap Syndrome?