THE IMPACT OF ADJUVANT ATORVASTATIN THERAPY ON PNEUMONIA OUTCOME: A PROSPECTIVE STUDY OF CLINICAL AND INFLAMMATORY RESPONSES IN RELATION TO MORTALITY REDUCTION

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Abstract

Introduction: pneumonia is still among the top three killers worldwide, new drug classes other than antibiotics are under investigations for more than 50 years, statins with their anti-inflammatory, immunomodulatory, and anti-oxidant effects may be a promising target in this paradigm.

Objective: to determine whether or not. adjuvant atorvastatin could improve the outcomes of pneumonia

Patients and methods: sixty pneumonia patients admitted to ain shams university hospitals were randomized into either ; *statin naive* n=30 (received antibiotics according to the egyptian scientific society of bronchology (ESSB) guidelines), and *statin users* n=30 (received antibiotics according to ESSB guidelines + atorvastatin 40mg once daily for 30 days). total leukocytic count (TLC), C-reactive protein (CRP) were measured, with estimation of pneumonia severity index (PSI) on the 1st day of diagnosis, and repeated on the 7th day, length of hospital stay and mortality were also recorded.

Results: statin users showed statistically significant more reduction of CRP *(p 0.038)*, with significantly shorter hospital stay *(p < 0.001)*. no difference in reduction magnitude of TLC *(p 0.217)* or PSI *(p 0.325)*, and finally no difference in mortality on comparing the two groups.

Conclusion: incorporating atorvastatin therapy with antibiotics in the treatment of pneumonia resulted in significantly lower CRP levels that were well-reflected by shorter hospital stay when compared to antibiotics alone.

Keywords: pneumonia, atorvastatin, inflammatory markers.

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List of Acronyms Used

ABC	adenosine triphosphate binding cassette
ADM	adrenomedullin
ALT	alanine transaminase
APACHE	acute physiology and chronic health evaluation
APR	acute-phase reactant
ARDS	acute respiratory distress syndrome
AST	aspartate transaminase
ATP	adenosine triphosphate
ATS	American thoracic society
AVP	arginine-vasopressin
BAL	bronchoalveolar lavage
C.pneumoniae	chlamydia pneumoniae
CAP	community-acquired pneumonia
CARS	compensatory anti-inflammatory response
CBC	complete blood count
CKD	chronic kidney disease
CMV	cytomegalovirus
COPD	chronic obstructive pulmonary disease
CPIS	clinical pulmonary infection score
CK	creatine kinase
CRB-65	confusion, respiratory rate, blood pressure, 65
CRP	C-reactive protein
CT	computerized tomography
CURB-65	confusion, urea, respiratory rate, blood pressure, 65
DNA	deoxyribonucleic acid
EBV	Epstein–Barr virus
EPIC	etiology of pneumonia in the community
ESBL	extended spectrum β lactamase

ESR	erythrocyte sedimentation rate
ESSB	Egyptian scientific society of bronchology
FFP	farnesylpyrophosphate
FiO_2	fraction of inspired oxygen
GGPP	geranylgeranylpyrophosphate
GTPases	guanosine triphosphatases
H.influenza	haemophilus influenza
HAP	hospital-acquired pneumonia
HCAP	healthcare-associated pneumonia
HDL	high density lipoproteins
HIV	human immunodeficiency virus
HMG-CoA	hydroxy methylglutaryl coenzyme A
ICU	intensive care unit
IDSA	infectious diseases society of America
IHD	ischemic heart disease
IL-10	interlukin-10
IL-1β	interleukin-1β
IL-6	interleukin-6
IM	intramuscular
iNOS	inducible nitric oxide synthase
IQR	interquartile range
IRVS	intensive respiratory or vasopressor support
IV	intravenous
LDL	low density lipoproteins
LDLR	low density lipoprotein receptor
LRTIs	lower respiratory tract infections
M.pneumoniae	mycoplasma pneumoniae
M.tuberculosis	Mycobacterium tuberculosis
MAP	mitogen-activated protein
MDR	multidrug resistant
MHC-II	major histocompatibility complex class II
MRSA	methicillin-resistant Staphylococcus aureus

NADPH	nicotinamide adenine dinucleotide phosphate-H
NFkB	nuclear factor kappa B
PAMPs	pathogen associated molecular patterns
PaO_2	partial pressure of oxygen
PAP	Papanicolaou stain
PCR	polymerase chain reaction
PCT	procalcitonin
PORT	pneumonia patient outcomes research team
PRRs	pattern recognition receptors
PSI	pneumonia severity index
Ras	rat sarcoma
RBCs	red blood cells
S.aureus	staphylococcus aureus
S.pneumoniae	streptococcus pneumoniae
SARS	severe acute respiratory syndrome
SCAP	severe community-acquired pneumonia
SIRS	systemic inflammatory response syndrome
SLE	systemic lupus erythematosus
SMART-COP	systolic blood pressure, multilobar chest radiography involvement, serum albumin, respiratory rate, tachycardia, confusion, oxygenation, arterial pH
SR-A	class A scavenger receptor
SR-BI	scavenger receptor B type I
sTREM-1	soluble triggering receptor expressed on myeloid cells-1
TLC	total leukocytic count
TLR	toll-like receptor
TNFα	tumor necrosis factor α
ULN	upper limit of normal
VAP	ventilator-associated pneumonia
WBCs	white blood cells
WHO	world health organization

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Pneumonia is defined as inflammation of the pulmonary parenchyma caused by an infectious agent, it may present with fever or hypothermia, sweating, rigors, and pulmonary symptoms such as cough, sputum production, shortness of breath, chest pain, in addition to pulmonary lesions observed on radiographic examination.(1)

The diagnosis and management of pneumonia has been complicated by the discovery of new pathogens, expanded antimicrobial resistance, increased population of immunocompromised patients, novel diagnostic tools and antimicrobial agents.(1)

According to the latest estimates of the world health organization (WHO); lower respiratory tract infections (LRTIs) including pneumonia remain among the top 3 killers worldwide, after ischemic heart disease (IHD), and stroke; causing about 3.2 million deaths in 2015. Also it is the number one killer in low-income countries (85 deaths per 100000 population).(2)

In Egypt, LRTIs were the cause of mortality in 14100 deaths (2012), and is ranked as the 9th among the top 10 killers; causing 2.7% of all mortalities.(3)

There is reinforcement of the classical concept that some pneumonia deaths were not due to failure to eradicate the

microorganism causing community-acquired pneumonia (CAP), but are closely related to inadequate host response. Excessive cytokine response in patients with severe CAP has been linked in many previous studies with deleterious effects and poor prognosis.[4]

Since the fifties of the 20th century, only a few antibiotics were added to the treatment arsenal of infections, without any new drug class other than antibiotics being added in the last 70 years.[5]

In this context, the use of immunomodulation appears to be an appealing option for improving prognosis in CAP. Theoretically, an anti-inflammatory treatment given with antibiotic therapy could prevent an excessive inflammatory response, improving the prognosis of severe CAP episodes.[6]

That's why; the use of anti-inflammatory drugs as adjuvant therapy with antibiotics is taking a reasonable share of research in the filed of sepsis and inflammatory diseases. the agents used so far include corticosteroids, statins, macrolides, angiotensin converting enzyme inhibitors, and toll-like receptor antagonists.[5]

Statins with their powerful anti-inflammatory, immunomodulatory, and anti-oxidant properties (due to interference with mevalonate pathway) make them candidate

members to be used in the management of sepsis and different types of infections including pneumonia.[7]

The aim of this study was to evaluate the impact of adjuvant atorvastatin therapy on pneumonia outcomes.

Chapter (1): Pneumonia

Pneumonia is defined as inflammation of the pulmonary parenchyma caused by an infectious agent, it may present with constitutional manifestations like fever or hypothermia, sweating, rigors, and pulmonary symptoms such as cough, sputum production, shortness of breath, chest pain, in addition to pulmonary lesions observed on radiographic examination.(1)

History of pneumonia

Pneumonia has been known since the earliest records of medicine and is one of the oldest diseases to have a specific diagnosis and name, The Greeks gave the name pneumonia, meaning “inflammation of the lung”, with its root "pneumon" meaning lung or derived from "pleumon" that means floater or "pnein" that means to breathe. It had been found in Egyptian mummies (1250-1000 BC), with a case of pneumonia that contained a bacillus that resembled yersenia pestis, and another case of pneumonia with hepatization.(8)

Hippocrates (460-370 BC) recommended bleeding and clysters (enema) for pneumonia with pleurisy, depending on the site of pain, as well as age, color of the patient, and the season of the year. Physicians also recognized that the “crisis” represented a crucial and dramatic point, designating a victory over the disease.(8)

Aretaeus of cappadocia in the second century recognized the grave danger of pneumonia and noted- as hippocrates did- that death often came on the 7th day, also he mentioned the membrane surrounding the lung and its inflammation "pleurisy" which “if it takes a favorable turn, the resolution occurs on the 14th day, but if not so, it is converted into empyems.”[8]

Celsus (25 BC-50 AD)- whose work was made known by Pope Nicholas V (1397-1455)- had accurately described pneumonia and its treatment with bleeding (venesection), light diet, exposure to bright light, and repeated changes of the room air.[8]

Rene Laennec (1781-1826) wrote about pneumonia; and in 1819 described the use of the stethoscope to make the diagnosis; with crepitus at the onset of the disease and its gradual fading when hepatization occurred, he also described moist rales, puerile breathing, pectoriloquy and aegophony in the diagnosis of pneumonia and other pulmonary diseases.[8]

In August 1928, a rewarding event in the treatment of pneumonia occurred; Alexander Fleming had identified penicillin in a laboratory mold that contaminated his petri dishes destroying staphylococci colonies, and here comes the spark where the revolution of antibiotics started. Although this did not come to fruition unless 15 years later where the team of Florey and Chain at Oxford, re-discovered Fleming's publication and made major efforts to produce large quantities of penicillin.[8]

Epidemiology

Some authors refer to pneumonia as the forgotten killer, according to the latest WHO estimates; LRTIs including pneumonia remain among the top three killers worldwide (Figure 1), after IHD, and cerebrovascular stroke; causing about 3.2 million deaths in 2015. Also it is the number one killer in low-income countries (85 deaths per 100000 population) (Figure 2), the 3rd in the list for lower-middle income countries (52 deaths /100000 population), the 5th in upper-middle income countries with 27 deaths/100000, and the 6th in high-income countries causing 38 deaths/100000.(2)

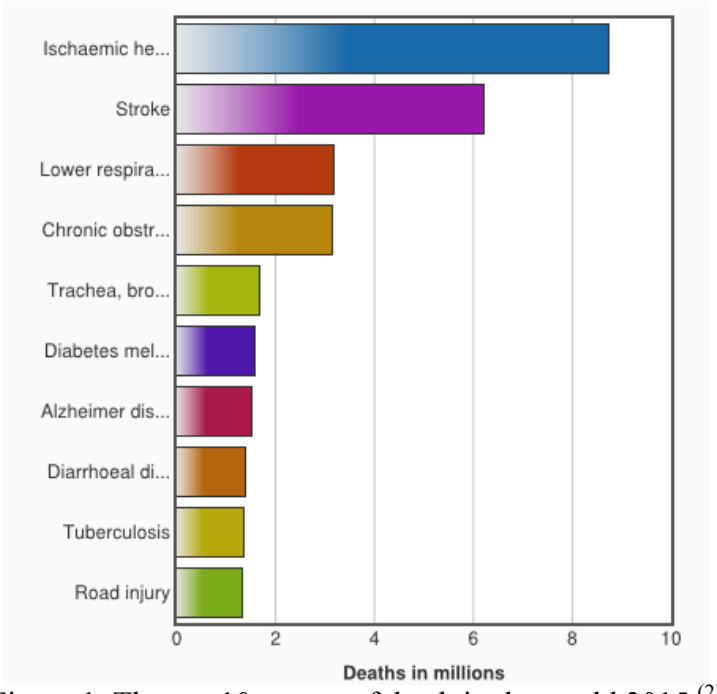

Figure 1. The top 10 causes of death in the world 2015.(2)