GRAM NEGATIVE INFECTIONS IN THE INTENSIVE CARE UNIT

Essay

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ALI	acute lung injury
ALT	alanine aminotransferase
APACHE	Acute physiology and chronic health evaluation
APC	Activated protein C
AQP4	aquaporin 4
ARDS	acute respiratory distress syndrome
AST	aspartate transaminase
BBB	Blood Brain Barrier
BP	Blood pressure.
C1	complement fragment 1
C5a	complement fragment 5a
C5aR	complement fragment 5a receptor
C5b-9complexes	terminal or late acting complement proteins
CCR2	chemokine receptor 2
CDC	Centers for Disease Control and Prevention
CD14, MD2, toll-like receptors 2 and 4, and Fc-gamma receptors II and III	cell surface receptors
cGMP	cyclic guanosine monophosphate
cNOS/ NOS3	Constitutive nitric oxide synthase
CVP	central venous pressure
CVVH	Continuous venovenous hemofiltration
DIC	disseminated intravascular coagulation
ED	Emergency Department
EDTA	Disodium edetate
eNOS	endothelial nitric oxide synthase
ESBL	Extended spectrum beta-lactamases
ESICM	European Society of Intensive Care Medicine
ESKAPE	Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae,Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacter spp
G-CSF	granulocyte colony-stimulating factor

GI	gastrointestinal
HAI	Hospital acquired infections
HCW	health care worker
ICAM-1	intercellular adhesion molecule-1
ICU's	intensive care units
IIT	intensive insulin therapy
IL-1	Interleukin-1.
IM	inner membrane
iNOS/ NOS2	Inducible nitric oxide synthase
IPP	inspiratory plateau pressure
ISF	International Sepsis Forum
LBP	Lipid-binding protein
LMWH	low molecular weight heparin
LPS	lipopolysaccharide
MAC	membrane attack complex
MAP	mean arterial pressure
MDR	multi-drug resistant
MODS	Multiple organ dysfunctions
MOF	multiple organ failure
MRSA	methicillin-resistant *Staphylococcus aureus*
MyD88	myeloid differentiation factor 88
nAChR	nicotinic acetylcholine receptor
NF-κb	Nuclear factor-κb.
NNIS	National Nosocomial Infections Surveillance.
nNOS/ NOS1	Neuronal nitric oxide synthase
NO	Nitric oxide.
NOD	nucleotide-oligomerization domain
NOS	nitric oxide synthase
OM	outer membrane
OMPs	outer membrane proteins
OMVs	Outer membrane vesicles
PAMPs	pathogen-associated molecular patterns
PCO_2	Partial pressure of CO_2
PECAM	platelet endothelial cell adhesion molecule
PEEP	Positive end expiratory pressure

PMNs	Polymorphonuclear leukocytes
Ppao	pulmonary artery occlusion pressure
PRRs	Pattern recognition receptors
PS	Polysaccharide
PT	prothrombin time
PTT	partial thromboplastin time
RCTs	Randomized controlled trials.
rhAPC	recombinant human activated protein C
rhMFG-E8	Recombinant Human Milk Fat Globule Epidermal Growth Factor 8
RIG-I	retinoic-acid-inducible gene I.
ROS	reactive oxygen species
SARS	severe acute respiratory syndrome
SBT	Spontaneous breathing trials
SCCM	Society of Critical Care Medicine
$ScvO_2$ and SvO_2	Central or mixed venous oxyhemoglobin saturation
SIRS	systemic inflammatory response syndrome
SNP	single nucleotide polymorphism
SSC	Surviving Sepsis Campaign
SVR	systemic vascular resistance
TIR	Toll-IL-1 resistance
TLRs	Toll-like receptors.
TNFα	tumor necrosis factor alpha
TRIF	TIR-domain-containing adaptor molecule 1
UFH	unfractionated heparin
VCAM-1	vascular cell adhesion molecule-1
VRE	vancomycin-resistant enterococci
WHO	World Health Organization

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Introduction

Infections caused by gram negative bacilli typically occur in the lungs, the urinary tract, at surgical sites and in the blood stream. They are considered a significant cause of morbidity and mortality. The gram negative bacilli most commonly responsible for infection in humans are Enterobacter *species***,** Klebsiella pneumoniae, Pseudomonas aeruginosa, Escherichia coli, Acinetobacter species, *and* Serratia marcescens. Depending on the site of infection and the patient's comorbid conditions, mortality related to infections caused by gram-negative bacilli ranges from 20 % to 60 % **(Sarah et al., 2011).**

In prevalence study evaluating the extent and patterns of infection among more than 13 000 patients in ICU's around the world, 51% of patients had documented infection and 71% were receiving antimicrobial agents; gram-negative infections accounted for 63% of infections **(Vincent et al., 2009).**

Infections caused by gram-negative bacteria have features that are of particular concern. These organisms are highly efficient at up-regulating or acquiring genes that code for mechanisms of antibiotic drug resistance, especially in the presence of antibiotic selection pressure **(Boucher et al., 2009).**

The aim of the study

The aim of this essay is to cast light on the problem of gram negative infections in the intensive care unit with emphasis on their prevalence, pathogenesis, diagnosis, treatment and available strategies for their prevention.

Epidemiology of gram negative sepsis

Prior to the 1980's, gram negative bacilli were the predominant organisms associated with nosocomial blood stream infections in the United States. Since then, gram-positive aerobes (e.g., coagulase negative staphylococci, staphylococcus aureus, and enterococcus) and Candida species have increased in relative importance. In 1975, hospitals that participated in the National Nosocomial Infections Surveillance (NNIS) System reported that gram negative bacilli were responsible for 55 % of bacteremia hospital wide. By 2003, NNIS hospitals reported that gram negative bacilli were responsible for 24 % of nosocomial bacteremia in intensive care units (ICUs) **(Gaynes and Edwards, 2005).**

However, a surveillance study of hospital wide primary health care associated blood stream infections in a large tertiary care hospital in the United States found a significant increase in the rate of gram negative bacillary blood stream infections in 2003 which may represent either a reemergence of gram-negative infections over the past five years or changes in patient demographics in that institution **(Albrecht et al., 2006).**

The proportion of gram negative organisms identified in blood stream infections increased significantly from 15.9 % in 1999 to 24.1 % in 2003. No specific gram negative species contributed disproportionately to the increase and with few exceptions there were no significant increases in antimicrobial resistance to explain this trend. This study excluded bloodstream infections that were community-acquired or were secondary to infection at another site. In Latin America, and some areas of Europe and the Far East, the proportion of bacteremia caused by gram-negative bacilli is greater than that identified in the United States this geographic difference in etiology of bacteremia is illustrated by the following studies: **(Biedenbach et al., 2004).**

A prospective study of bloodstream infections in hematologic malignancy patients from Brazil hospitalized between January 2000 and June 2001 identified gram-negative bacteria in 81 of 133 (61 %) episodes **(velasco et al., 2003).** In contrast, studies from North America have generally shown a predominance of gram-positive bacteria **(Gaynes and Edwards, 2005).**

A prospective multicenter study in Italy conducted between 1999 and 2000 found 46 % of bacteremia was due to gram negative bacilli in this study; gram negative bacilli were the etiologic agent in 42 % of hospital-acquired bacteremia and 55 % of community-acquired bacteremia **(luzzaro et al., 2002).**

A retrospective review of 238 episodes of bacteremia in patients ≥ 65 years of age in the United States identified gram-negative bacilli as the etiologic agent in 36 % of cases; 81 % of patients were admitted with bacteremia from home **(greenberg et al .,2005).** The rate of gram-negative bacteremia in patient's ≥ 65 years is even higher in nursing home residents as illustrated by a retrospective review of 169 episodes of bacteremia identified between January 1997 and April 2000 Of the 132 episodes of monomicrobial bacteremia, 78 (59 %) were caused by gram-negative organisms. Thus, even within North America, there are subpopulations of patients in whom gram-negative bacteremia occurs more frequently than does gram-positive bacteremia **(mylotte et al., 2002).**

Risk factors

Most hospitalized patients with gram negative bacteremia have at least one comorbid condition a study of 326 episodes of gram negative bacteremia at two universities-affiliated medical centers identified comorbid conditions in 315 (97 %) Conditions identified in this and other studies included**:**

- Hematopoietic stem cell transplant
- Liver failure
- Serum albumin <3 mg/dL
- Solid organ transplant
- Diabetes
- Pulmonary disease
- Chronic hemodialysis
- HIV infection
- Hematologic malignancy
- Treatment with glucocorticoids
- Elderly

(Thomsen et al., 2005).

In addition to these risk factors, combat injured military personnel and patients injured during natural disasters involving trauma in water are also at increased risk for infections caused by gram-negative bacilli **(Kallman et al., 2006).**

Source of infection

The source of infection differs depending on the patient population studied as illustrated in the following studies:

In the retrospective review of nursing home residents noted above, the following were identified as the most common sources of infection in the cases of gram-negative bacteremia**:**

- Urinary tract 81 %
- Gastrointestinal tract 9 %
- Respiratory tract 4 %
- others 6 %

In a retrospective review of gram-negative bacteremia in the elderly (eg, >70 years), the most common sources of infection in community-acquired infection were:

- Urinary tract 50 %
- Gastrointestinal tract 27 %
- Respiratory tract 10 %
- Skin and soft tissue 8 %
- Others 5 %

A similar distribution was noted for hospital-acquired infection **(Mylotte et al., 2002).**

The source of infection differs in patients admitted to the ICU; a retrospective study found the following most common sources in this patient population:

- Respiratory tract 49 %
- Central venous catheter 16 %
- Gastrointestinal tract 4 %
- Urinary tract 2 %
- others 29 %

Identifying the most likely source of infection impacts on empiric antibiotic treatment because the most likely microbiologic agent responsible may differ by source of infection **(Sligl et al., 2006).**

Causative organisms

Data from the National Nosocomial Infections Surveillance (NNIS) System stated that the most common gram negative species isolated during gram-negative bacteremia included:

- Enterobacter species 18.5 %
- Klebsiella pneumoniae 17.8 %
- Pseudomonas aeruginosa 14.4 %
- Escherichia coli 13.6 %
- Acinetobacter species 10.1 %
- Serratia marcescens 9.7 %

(Gaynes and Edwards, 2005).

The order of most common gram negative bacilli in blood stream infections in community acquired cases differs from those responsible for hospital acquired cases. This is illustrated by the Italian study noted above which identified the following list of the most common gram negative organisms isolated during community acquired gram negative bacteremia

- E. coli 76 %
- P. aeruginosa 7.9 %
- K. pneumonia 5.4 %
- Proteus mirabilis 4.2 %
- Enterobacter species 3.7 %

(Luzzaro et al., 2002).