CURRENT ASPECTS OF ANTIBIOTIC TREATMENT AND ENDOTOXIN RELEASE

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Abstract

Endotoxin is a major cause of sepsis and organ failure in humans. Antibiotics, which are administrated to treat these severe infections, may release Endotoxin from the bacterial wall and may harm the patient. Penicillin-binding protein (PBP) 2-specific antibiotics, e.g., imipenem were considered to release less amounts of free Endotoxin than PBP 3-specific antibiotics, e.g., Ceftazidime. This effect has been contributed to an increased bactericidal activity of PBP 2-specific antibiotics and consecutive change in morphology of pathogens, enabling phagocytosis. Recent in vitro studies, however, were unable to repeat these results. The antibiotic-induced Endotoxin release may change with the type of pathogen and dosing of the antibiotic. In animal studies Endotoxin release did not show a correlation to the bactericidal effect in all experiments. Antibiotic-induced Endotoxin release and outcome was different with regard to animal models, location of infection, strains, pharmocodynamics and dosage of antibiotics. Bacteriostatic antibiotics, e.g., lincomycin and clindamycin, were able to induce Endotoxin release. In some studies imipenem caused either similar release of Endotoxin compared to ceftazidime or more compared to ciprofloxacin. Chemically modified tetracycline or combination of antibiotics prevented an increased Endotoxin release. In patients with urosepsis controversial results were observed when imipenem was compared to ceftazidime. In clinical observational studies or post-hoc analysis of a randomized clinical trial a differential release of Endotoxin after imipenem and cephalosporins has been reported. In conclusion, antibiotic-induced Endotoxin release may be clinically relevant. However, there are many interfering factors in clinical studies, which need to be addressed properly when analyzing studies on antibiotic-induced Endotoxin release.

Key words
Antibiotic-induced endotoxin release, LPS

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›Resumen

La endotoxina es una de las causas principales de sepsis e insuficiencia multiorgánica en los seres humanos. Los antibióticos que se administran para tratar estas infecciones graves pueden liberar endotoxina de la pared bacterial y afectar al paciente. Se consideraba que los antibióticos específicos de la proteína ligadora de penicilina (PLP) 2, por ejemplo, imipenem, liberaban menores cantidades de endotoxina libre que los antibióticos específicos de la PLP 3, como la ceftazidima. Este efecto contribuye al aumento de la actividad bactericida de los antibióticos específicos de la PLP 2, con los consiguientes cambios en la morfología de los patógenos, lo que posibilita la fagocitosis. Sin embargo, recientes estudios *in vitro* no pudieron repetir estos resultados. La liberación de endotoxina inducida por antibióticos puede cambiar con el tipo de patógeno y la dosificación del antibiótico. En estudios con animales, la liberación de endotoxina no se correlacionó con el efecto bactericida en todos los experimentos. La liberación de endotoxina inducida por antibióticos, así como los resultados, fue diferente según los modelos con animales, la localización de la infección, las cepas, la farmacodinamia y la dosificación del antibiótico. Los antibióticos bacteriostáticos, como lincomicina y clindamicina, indujeron la liberación de endotoxina. En algunos estudios la liberación de endotoxina inducida por imipenem fue similar a la causada por ceftazidima y mayor que la inducida por ciprofloxacina. Las tetraciclinas modificadas químicamente y la combinación de antibióticos evitaron el aumento en la liberación de endotoxinas. En pacientes con urosepsis se observaron resultados controvertidos al comparar imipenem con ceftazidima. En estudios clínicos de observación o en los análisis *post hoc* de ensayos clínicos aleatorizados se informaron diferencias en la liberación de endotoxina luego de la administración de imipenem y cefalosporinas. En conclusión, la liberación de endotoxina inducida por antibióticos podría ser clínicamente relevante. No obstante, en los estudios clínicos pueden interferir muchos factores que deben ser abordados debidamente cuando se analizan los estudios acerca de este tema.

›Palabras clave

Liberación de endotoxina inducida por antibióticos, lipopolisacáridos

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CURRENT ASPECTS OF ANTIBIOTIC TREATMENT AND ENDOTOXIN RELEASE

Endotoxin is one of the major pathogenic causes of gram-negative sepsis in humans.[1] The clinical significance of endotoxin and its association with mortality has been demonstrated in several studies.[2-6] Recent reviews discussed drug-induced, e.g., antibiotic, fever as possible cause of fever of unknown origin.[7,8] Since Jackson and Kropp (1992) demonstrated that Penicllin-binding Protein (PBP) 2-specific antibiotics (Imipenem) may release less free endotoxin than PBP 3-specific antibiotics (ceftazidime) which has been associated with a filamentation of the pathogen, it has been assumed that antibiotics may have a different potential to release endotoxin and to influence the outcome of septic patients.[9] However, other bacterial wall compounds, Lipoteichoic acid (LTA), may be involved in the host response after antibiotic treatment.[10]

In vitro studies

Most studies were performed in vitro with different pathogens and antibiotics. The effect of penicillin has been investigated in *Neisseria* meningitis, *Streptococcus* group A, *Staphylococcus aureus*, *Meningococcus*, and *Streptococcus faecium*. In most trials penicillin released lipopolysaccharide (LPS), LTA, IL-1 and TNF-alpha. (table 1).

Table 1: Effects of penicillin on in-vitro endotoxin/cytokine/protein release

Year	Author	Pathogen or cell	Endotoxin/cytokine/protein release
1980	Anderssen[11]	N meningitis	LPS+
1981	Kessler[12]	S group A	LTA, sLTA +
1985	Gold[13]	S faecium	IL-1 +
1986	Nealon[14]	S group A, S aureus	LTA +
1987	Kiriyama[15]	S aureus	LTA +
1991	Mellado[16]	N meningitis	LPS+
1992	Iino[17]	LPS	TNF +
1997	Prins[18]	Meningococcus	LPS-

LPS Lipopolysaccharide; LTA Lipoteichoic acid; IL-1 Interleukin-1; TNF-alpha Tumor Necrosis Factor alpha

The effect of aminoglycoside therapy on endotoxin release has been studied mainly in *E. coli*, *K. pneumoniae*, *P. aeruginosa*, *H. influenzae*, *E. cloacae*, *S. aureus*, *Salmonella* spp., and *Neisseria* spp. Depending on pathogen gentamicin was able to increase or decrease endotoxin release or it showed no effect when compared to controls. Most studies reported a decrease in TNF-alpha release after treatment with an aminoglycoside. Tobramycin lead to a decreased release of LPS and amikacin induced a decrease in LPS and TNF release (table 2).

Table 2: Effects of amikacin/gentamicin on in-vitro endotoxin/cytokine/protein release

Year	Author	Aminoglycoside	Pathogen or cell	Endotoxin/cytokine/protein release
1975	Rusmin[19]	G	E coli, K pneumoniae, P aeruginosa	LPS+
1985	Shenep[20]	G	E coli	LPS+
1986	Cohen[21]	G	E coli	LPS-
1989	Stokes[22]	G		TNF +
1991	Simon[22]	A	E coli, THP cell	TNF-
1992	Bingen[23]	A	H influenzae	LPS-
1992	Van den Berg[24]	G	E coli	LPS+
1993	Eng[25]	G	E coli K pneumoniae E cloacae P aeruginosa S aureus	LPS- LPS- No effect No effect No Endotoxin
1993	Evans[26]	G	E coli	LPS+
1994	Crosby[27]	T	E coli, E cloacae	LPS-
1995	Prins[28]	G	E coli	TNF-
1996	Lamp[29]	A	E coli, P aeruginosa	LPS-
1998	Van Langevelde[30]	G	S aureus	LTA, PG +
1998	Trautmann[31]	T	E coli	LPS-
2000	Sjolin[33]	T	E coli	LPS-
2001	Xu[34]	A	P aeruginosa, E coli	LPS-
2002	Bentley[35]	A	E coli, whole blood	LPS-, TNF-
2002	Krehmeier[36]	G	PBMC	TNF-
2003	Tsumura[37]	G	E coli	LPS+
2003	Goscinski[38]	T	E coli, Klebsiella, Salmonella, Neisseria	LPS-

LPS Lipopolysaccharide; LTA Lipoteichoic acid; IL-1 Interleukin-1; TNF-alpha Tumor Necrosis Factor alpha
G gentamicin; A amikacin; T tobramycin

In most studies imipenem, the compound which was studied best was able to decrease endotoxin release or TNF-alpha/Il-6 release. However, in recent trials[35,39] imipenem either increased endotoxin/TNF-alpha release or had no effect (table 3).

Table 3: Effects of imipenem on in-vitro endotoxin/cytokine/protein release

Year	Author	Pathogen or cell	Endotoxin/cytokine/protein release
1991	Simon[23]	E coli, THP cell	TNF-
1991	Dofferhoff[40]	E coli	LPS-
1992	Jackson[9]	P aeruginosa	LPS-
1993	Arditi[41]	H influenzae	TNF-
1993	Evans[16]	E coli	LPS+
1993	Dofferhoff[42]	E coli	TNF 4h similar, 24h -
1993	Eng[23]	E coli, K pneumoniae, E cloacae, P aeruginosa S aureus	LPS- LPS- LPS- LPS- No endotoxin
1995	Prins[28]	E coli, whole blood	LPS-, TNF-, IL-6-
1996	Yokochi[43]	P aeruginosa	LPS-
1996	Inoue[44]	E coli, S aureus, E cloacae, C freundii, P aeruginosa, S maltophilia	LPS-
1996	Lamp[29]	E coli, P aeruginosa	LPS-
1997	Narita[45]	P aeruginosa	LPS-
1997	Arditi[46]	E coli	IL-6-
1997	Takahashi[47]	E coli	LPS-
1998	Trautmann[31]	E coli	LPS-
1998	Van Langevelde[48]	S typhi	No difference
1998	Horii[49]	E coli, S marcescens, K pneumoniae, P aeruginosa, P mirabilis, P vulgaris	LPS- (exception P aeruginosa)
1998	Trautmann[30]	P aeruginosa	LPS-
1999	Yamaguchi[31]	P aeruginosa	LPS-
1999	Trautmann[37]	E coli, Monocyte	LPS-, TNF-
1999	Horii[33]	P aeruginosa	LPS-
2000	Cui[34]	E coli, S aureus	TNF+ release in co-culture with S aureus
2001	Xu[24]	P aeruginosa, E coli	LPS-
2002	Bentley[35]	E coli, whole blood	LPS+, TNF+
2003	Tsuji[37]	P aeruginosa	LPS no difference

LPS Lipopolysaccharide; IL-1 Interleukin-1; TNF-alpha Tumor Necrosis Factor alpha; IL-6 Interleukin-6

Ceftazidime is the compound used in most in-vitro studies on endotoxin release. In the majority of studies endotoxin or proinflammatory cytokines, e.g., TNF-alpha, IL- 6 and IL-1 were increased when ceftazidime was used for treatment. However, ceftazidime decreased LPS-release from *P. aeruginosa*[25] or did not show a difference compared to untreated controls[37,49] (table 4).

Table 4: Effects of ceftazidime on in-vitro endotoxin/cytokine/protein release

Year	Author	Pathogen or cell	Endotoxin/cytokine/protein release
1991	Simon[23]	E coli, THP cell	TNF+
1991	Dofferhoff[46]	E coli	LPS+
1992	Jackson[9]	P aeruginosa	LPS+
1993	Evans[16]	E coli	LPS+
1993	Dofferhoff[47]	E coli	TNF+
1993	Eng[25]	E coli, K pneumoniae, E cloacae, P aeruginosa S aureus	LPS+ or no effect LPS+ or no effect LPS+ or no effect LPS- No Endotoxin
1994	Bucklin[33]	E coli	LPS+
1994	Leeson[36]	Monocytes E coli	TNF+
1995	Prins[28]	E coli, whole blood	LPS+, TNF+, IL-6+
1996	Inoue[44]	E coli, S aureus, E cloacae, C freundii, P aeruginoase, S maltophilia	LPS+
1996	Lamp[19]	E coli, p aeruginosa	LPS+
1997	Narita[45]	P aeruginosa	LPS+
1998	Trautmann[31]	E coli	LPS+
1998	Van Langevelde[48]	S typhi	LPS no difference
1998	Horii[49]	E coli, S marcescens, K pneumoniae, P aeruginosa, P vulgaris, P mirabilis	LPS+ (exception P aeruginosa)
1998	Trautmann[30]	P aeruginosa	LPS+
1999	Kishi[37]	E coli	LPS+, TNF+, IL-1+
1999	Yamaguchi[31]	P aerugnosa	LPS+
1999	Trautmann[32]	E coli, Monocyte	LPS+, TNF+
2000	Horii[38]	E coli	LPS+
2001	Xu[24]	P aeruginosa, e coli	LPS+
2003	Tsuji[27]	P aeruginosa	LPS no difference
2003	Liang[39]	P aerugnosa, RAW cells	LPS+, TNF+

LPS Lipopolysaccharide; IL-1 Interleukin-1; TNF-alpha Tumor Necrosis Factor alpha

The best studied quinolones are ciprofloxacin and ofloxacin. In the some recent studies ciprofloxacin or ofloxacin were responsible for a decrease in endotoxin release or TNF-alpha/IL-6 release. However, some investigators reported an increase in endotoxin and/or proinflammatory cytokine release[17,21,24,28,29] (table 5).

Table 5: Effects of ciprofloxacin/ofloxacin on in-vitro endotoxin/cytokine/protein release

Year	Author	Quinolone	Pathogen or cell	Endotoxin/cytokine/protein release
1986	Cohen[21]	C	E coli	LPS+
1991	Simon[23]	C	E coli, THP cell	TNF intermediate
1992	Iino[17]	O	Monocytes	TNF+
1992	Van den Berg[24]	C	E coli	LPS+
1993	Eng[25]	C O 	E coli, K pneumoniae, E cloaecae, P aeruginosa S aureus	LPS- LPS- LPS- LPS+ or no effect No endotoxin
1994	Crosby[27]	C	E coli, E cloacae	LPS+
1995	Prins[28]	C	E coli, whole blood	LPS+, TNF+, IL-6+
1996	Lamp[29]	O	E coli, P aeruginosa	LPS-
1998	Trautmann[31]	C	E coli	LPS-
1999	Trautmann[52]	C	E coli	LPS-
2002	Krehmeier[36]	O C	PBMC PBMC	TNF-, IL-6- TNF-

LPS Lipopolysaccharide;, IL-1 Interleukin-1; TNF-alpha Tumor Necrosis Factor alpha; IL-6 Interleukin-6
C ciprofloxacin; O ofloxacin

Clindamycin and erythromycin were able to reduce the release of LPS and pro-inflammatory cytokines in gram-negative pathogens, but also lipoteichoic acid (LTA) and proinflammatory cytokines in gram-positive pathogens in most studies (table 6).

Table 6: Effects of clindamycin/erythromycin on in-vitro endotoxin/cytokine/protein release

Year	Author	Antibiotic	Pathogen or cell	Endotoxin/cytokine/protein release
1986	Nealon[14]	C	S group A, S aureus	LTA S aureus -
1992	Iino[17]	E	Monocytes	TNF-
1995	Khair[60]	E	H influenzae, HBEC	IL-6 -, IL-8 – sICAM-1 -
1998	Van Langevelde[30]	E C	S aureus, whole blood	LTA -, PG unchanged, TNF -, IL-10 -
1999	Kishi[57]	C	E coli	LPS -, IL-1 -, TNF -
2000	Orman[61]	C	S pneumoniae, murine macrophages	iNOS -, TNF-
2000	Horii[58]	C	E coli	LPS-
2003	Gerber[62]	C	S pneumoniae	LTA -

E erythromycin, C clindamycin
HBEC human bronchial epithelial cells
LPS Lipopolysaccharide; LTA Lipoteichoic acid; IL-1 Interleukin-1; TNF-alpha Tumor Necrosis Factor alpha; IL-6 Interleukin-6; IL-8 Interleukin-8; IL-10 Interleukin-10; PG Peptidoglycan; iNOS inducible Nitric Oxide Synthase; sICAM-1 soluble Intercellular-Adhesion-Molecule 1

Animal studies

Endotoxin liberating strains were considered to be more virulent.[11] An increase in endotoxin plasma levels after antibiotic administration has been observed by Shenep in 1984.[63] In 1986 Walterspiel demonstrated that subinhibitory doses of Polymyxin B modulate the lethal effects of LPS.[64] Shenep (1985) postulated that the LPS release is dependent on the class of antibiotics and

does not correlate with the rate of bacterial killing.[20] Johnston reported in 1984 that the level of endotoxemia was higher in antibiotic-treated survivors than in animals dying without antibiotics.[65]

Pre-treatment in animal studies
Selective antibiotic decontamination resulted in increased LPS levels.[66,67] Pre-treatment with agents that altered gut contents reduced endotoxemia and mortality.[68] Elevated TNF-release may be associated with enhanced hemodynamic response but not with increased mortality.[69] Pre-treatment with erythromycin may have beneficial effects in *Candida albicans* infection.[70]

Mode of application, location of infection
LPS release is not only influenced by the mode of action of the antibiotic class, but also by dosage, pharmacodynamics.[71] Topically applied imipenem demonstrated a profound bactericidal effect, but also increased LPS/TNF-alpha release.[72] Meropenem may increase LPS-release and mortality, whereas imipenem does the opposite.[45] The morphological changes induced by imipenem treatment may help phagocytosis by peritoneal cells.[73] In a burn injury model imipenem released less LPS but there was no relationship to a bactericidal effect.[74] Imipenem induced highest levels of LPS in *B. fragilis* and *Fusobacterium* spp. Infection.[75] LPS release may no be influenced by the bactericidal effect: imipenem and ceftazidime had a similar bactericidal power in a rat sepsis model, but there was less LPS release after imipenem treatment.[76] In 2003, Tsuji et al. demonstrated that imipenem, doripenem, meropenem and ceftazidime induced similar serum levels of LPS.[37] Treatment of animals with intra-abdominal infection resulted in increased survival, decreased plasma and peritoneal fluid levels of cytokines. LPS release was higher after imipenem than after ciprofloxacin treatment.[77]

Meningitis
In meningitis cefotaxime, cefpirome, meropenem and gentamicin induced endotoxin release. However, untreated animals showed higher endotoxin levels.[78] In *H. influenzae* infection of the middle ear no LPS has been observed after treatment with ceftriaxone.[79] In rabbit *S. pneumoniae* meningitis initiation of therapy with clindamycin (protein- synthesis inhibition) and continuation with a combination of ceftriaxone (beta- Lactam antibiotic) decreased neuronal injury.[62] This has been supported by a further study by Bottcher (2004).[80]

Bacteriostatic and combination antibiotic treatment
Bacteriostatic antibiotics (lincomycin and clindamycin) induced LPS release compared to no treatment.[58] Doxycycline exerted its protective effect by inhibiting nitrate production in a BALB mouse LPS model.[81] Recent studies investigated the effect of other compounds, matrix metalloproteinase inhibitors – chemically modified tetracycline, which prevented acute lung injury after cardiopulmonary bypass.[82] These compounds can significantly preserve cardiac mechanical function during septic shock.[83] The combination treatment with other endotoxin- neutralizing compounds, e.g., lipopolyamines[84] or Bactericidal- Permeability-increasing-Protein (BPI21)[85] may help to prevent the cephalosporin-induced increase in LPS release and improve survival. Mice challenged by *E. coli* showed a change in LPS-induced cytokine production and improved survival when pre-treated by clindamycin.[86] Antibiotics resulted in a shift of LD50 of approximately 500-fold in *E. coli* mouse infection model.[87] In 2003, Tsumura demonstrated in a rabbit *E. coli* model that flomoxef and gentamicin reduced in-vivo plasma LPS, TNF-alpha and blood bacterial counts to comparable levels. LPS release may not be a problem if appropriate antimicrobial agents were used.[37]

Clinical studies
In 1983 Teklu reported on the beneficial effects of meptazinol, an opioid antagonist with agonist properties, which diminished the Jarisch-Herxheimer reaction after tetracycline treatment in a randomized study in patients with louse- borne fever.[88]

Meningitis
In *H. influenza* meningitis ceftriaxone treatment leads to a release of free LPS with an associated inflammatory response.[89] Intraventricular applied gentamicin may have caused release of LPS resulting in increased IL-1 concentrations and poor outcome of patients with *coliform* meningitis.[90]

Urosepsis
Several studies were performed in patients with urosepsis. Imipenem caused less LPS release, serum and urine cytokine levels when compared to ceftazidime.[91] An increased release of endotoxin and TNF was observed in patients with acute pyelonephritis. It might be responsible for the persistence of fever despite negative blood cultures.[92] In a RCT in patients with gram-negative urosepsis no difference was found in plasma endotoxin, proinflammatory cytokines within the first 8 hours after antibiotic treatment with imipenem or ceftazidime.[93]

Trauma and surgical intensive care patients
In trauma patients antibiotics that are associated with a greater release of endotoxin and TNF (aztreonam, ceftazidime, and cefotaxime) are associated with greater release of endotoxin and TNF, and a greater mortality.[4] In surgical intensive care patients a significant increase of endotoxin plasma levels were observed after treatment with cefotaxime and ceftriaxone when compared to ciprofloxacin, tobramycin, and imipenem.[94] Patients undergoing hepatic resection showed no elevation in peripheral blood endotoxin levels after treatment with cefmetazole, latamoxef, flomoxef, cefazolin, cefoperazone, cefotiam.
The authors concluded that the endotoxin has been scavenged from the blood.[95] In 2001 Byl et al. observed a similar effect on endotoxin and cytokine release in gram-negative infections when treated with ceftazidime and imipenem.[96] Maskin reported high plasma concentrations of LPS, IL- 6, and TNF-alpha after treatment with ceftazidime and imipenem in septic patients. However, TNF-alpha plasma levels were significantly less 4 hours after imipenem administration.[97] In aortic aneurysm repair, a clinical model for reperfusion-injury and associated endotoxin release, oral ofloxacin prophylaxis lead to alteration of endotoxin neutralizing capacity and IL-6 plasma levels, but had no effect on endotoxin plasma levels and other inflammatory mediators.[98] In melioidosis caused by *Burkholderia pseudomallei* treatment with imipenem reduced the plasma endotoxin release without affecting survival.[99] In burn patients' endotoxin and TNF release increased 2h after cefoperazone treatment when compared to imipenem[100] (table 7).

Table 7: Clinical studies in antibiotic-induced endotoxin release

Year	Author	Type of study	Type of infection	Antibiotics
1983	Teklu	RCT	Louse-borne relapsing fever	Tetracycline
1989	Arditi	Prospective observation	H influenzae meningitis	Ceftriaxone
1989	Mustafa	RCT	Coliform meningitis	Gentamicin
1995	Prins	RCT	Urosepsis	Imipenem Ceftazidime
1995	Mock	Post-hoc analysis	Trauma patients	Aztreonam Ceftazidime Cefotaxime
1996	Holzheimer	Prospective observational	Surgical intensive care	Ciprofloxacin Cefotaxime Tobramycin Ceftriaxone Vancomycin Imipenem
1999	Ishikawa	Prospective observation	Hepatic resection	Cefmetazole Latamoxef Flomoxef Cefazolin Cefoperazone Cefotiam
1999	Giamarellou-Bourboulis	Prospective observation	Acute pyelonephritis	Cefuroxime
2000	Simpson	RCT	Melioidosis caused by Burkholderia pseudomallei	Ceftazidime Imipenem
2000	Luchi	RCT	Gram-negative urosepsis	Ceftazidime Imipenem
2001	Byl	RCT	Gram-negative infection	Ceftazidime Imipenem
2001	Jaber[101]	Prospective observation		Gentamicin
2002	Maskin	RCT	Sepsis	Ceftazidime Imipenem
2003	Holzheimer	RCT	AAA repair	Ofloxacin Cefotiam
2004	Wang	RCT	Burn patients with gram-negative infection	Imipenem Cefoperazone

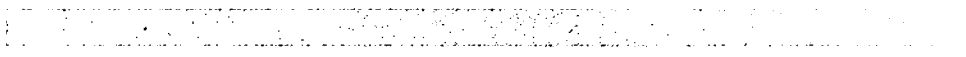
RCT randomized controlled trial

Summary

Endotoxin is a major cause of sepsis and organ failure in humans. Antibiotics are administrated to treat these severe infections. However, antibiotics may also do harm if not applied properly or may release Endotoxin from the bacterial wall, which may harm the patient. Penicillin-binding protein (PBP) 2-specific antibiotics, e.g., imipenem were considered to release less amounts of free Endotoxin than PBP 3-specific antibiotics, e.g., Ceftazidime. This effect has been contributed to an increased bactericidal activity of PBP 2-specific antibiotics and consecutive change in morphology of pathogens, enabling phagocytosis. Recent in vitro studies, however, were unable to repeat that result. The antibiotic induced Endotoxin release may be dependent on the strain and dosing of the antibiotic. In animal studies Endotoxin release was not influenced by the bactericidal effect. Antibiotic- induced Endotoxin release and outcome was different with regard to animal models, location of infection, strains, pharmacodynamics and dosage of antibiotics.

Bacteriostatic antibiotics, e.g., lincomycin and clindamycin, were able to induce Endotoxin release. Imipenem caused either similar release of Endotoxin compared to Ceftazidime or more compared to ciprofloxacin in some studies.

Chemically modified tetracycline or combination of antibiotics prevented an increased Endotoxin release. In patients with urosepsis controversial results were observed when imipenem was compared to Ceftazidime. In clinical observational studies or post-hoc analysis a differential release of Endotoxin after imipenem and cephalosporins has been reported. In conclusion, antibiotic-induced Endotoxin release may be clinically relevant. Analysis of clinical studies which failed to demonstrate the effect of antibiotic-induced Endotoxin release may help to plan further studies.



Bibliografía del artículo

1. Van Leeuwen PA, Boermeester MA, Houdijk AP et al. Clinical significance of translocation. Gut 1994; 35(1 Suppl):S28-34.
2. Svoboda P, Kantorova I, Ochmann J. Dynamics of interleukin 1, 2, and 6 and tumor necrosis factor alpha in multiple trauma patients. J Trauma 1994; 36(3):336-40.
3. Holzheimer RG, Schein M, Wittmann DH. Inflammatory response in peritoneal exudate and plasma of patients undergoing planned relaparotomy for severe secondary peritonitis. Arch Surg 1995; 130(12):1314-9.
4. Mock CN, Jurkovich GJ, Dries DJ et al. Clinical significance of antibiotic endotoxin-releasing properties in trauma patients. Arch Surg 1995; 130(11):1234-40.
5. Van Deuren M, Van der Ven-Jongekrijg J, Bartelink AK et al. Correlation between proinflammatory cytokines and antiinflammatory mediators and the severity of disease in meningococcal infections. J Infect Dis 1995; 172(2):433-9.
6. Kelly JL, O'Sullivan C, O'Riordain M et al. Is circulating endotoxin the trigger for the systemic inflammatory response syndrome seen after injury? Ann Surg 1997; 225(5):530-41.
7. Amin K, Kauffman CA. Fever of unknown orignin. Postgrad Med 2003; 114(3):69-75.
8. Roth AR, Basello GM. Approach to the adult patient with fever of unknown origin. Am Fam Physician 2003; 68(119):2223-8.
9. Jackson JJ, Kropp H. beta-Lactam antibiotic-induced release of ree endotoxin: in vitro comparison of penicillin-binding protein (PBP) 2-specific imipenem and PBP 3-specificic ceftazidime. J Infect Dis 1992; 165(6):1033-41.
10. Ginsburg I. Role of lipoteichoic acid in infection and inflammation. Lancet Infect Dis 2002; 2(3):171-9.
11. Andersen BM, Solberg O. Release of endotoxin from *Neisseria meningitides*. A short survey with a preliminary report on virulence in mice. NIPH Ann 1980; 3(2):49-55.
12. Kessler RE, Van de Rijn I. Effects of penicillin on group A streptococci: loss of viability appears to precede stimulation of release of lipoteichoic acid. Antimicrob Agents Chemother 1981; 19(1):39-43.
13. Gold MR, Miller CL, Mishell RI. Soluble non-cross-linked peptidoglycan polymers stimulate monocyte-macrophage inflammatory function. Infect Immun 1985; 49(3):731-741.
14. Nealon TJ, Beachey EH, Courtney HS et al.Release of fibronectin-lipoteichoic acid complexes from group A streptococci with penicillin. Infect Immun 1986; 51(2):529-35.
15. Kiriyama T, Miyake Y, Sugai M et al. Effects of mucopolysaccharides on penicillin-induced lysis of *Staphylococcus aureus*. J Med Microbiol 1987; 24(4):325-331.
16. Mellado MC, Rodríguez Contreras R, Mariscal A et al. Effect of penicillin and chloramphenicol on the growth and endotoxin release by *N. meningitides*. Epidemiol Infect 1991; 106(2):283-288.
17. Iino Y, Toriyama M, Kudo K et al. Erythromycin inhibition of lipopolysaccharide-stimulated tumor necrosis factor alpha production by human monocytes in vitro. Ann Otol Rhinol Laryngol Suppl 1992; 157:16-20.
18. Prins JM, Speelman P, Kuijper EJ et al. No increase in endotoxin release during antibiotic killing of meningococci. J Antimicrob Chemother 1997; 39(1):13-18.
19. Rusmin S, DeLuca PP. Effect of antibiotics and osmotic change on the release of endotoxin by bacteria retained on intravenous inline filters. Am J Hosp Pharm 1975; 32(4):378-80.
20. Shenep JL, Barton RP, Mogan KA. Role of antibiotic class in the rate of liberation of endotoxin during therapy for experimental gram-negative bacterial sepsis. J Infect Dis 1985; 151(6):1012-8.
21. Cohen J, McConnell JS. Release of endotoxin from bacteria exposed to ciprofloxacin and its prevention with polymyxin B. Eur J Clin Microbiol 1986; 5(1):13-7.
22. Stokes DC, Shenep JL, Fishman M et al. Polymyxin B prevents lipopolysaccharide-induced release of tumor necrosis factor-alpha from alveolar macrophages. J Infect Dis 1989; 160(1):52-7.
23. Simon DM, Koenig G, Trenholme GM. Differences in release of tumor necrosis factor from THP-1 cells stimulated by filtrates of antibiotic-killed *Escherichia coli*. J Infect Dis 1991; 164(4):800-2.
24. Bingen E, Goury V, Bennani H et al. Bactericidal activity of beta-lactams and amikacin against *Haemophilus influenzae:* effect on endotoxin release. J Antimicrob Chemother 1992; 30(2):165-72.
25. Van den Berg C, de Neeling AJ, Schot CS et al. Delayed antibiotic-induced lysis of *Escherichia coli* in vitro is correlated with enhancement of LPS release. Scand J Infect Dis 1992; 24(5):619-27.

26. Eng RH, Smith SM, Fan-Havard P et al. Effect of antibiotics on endotoxin release from gram-negative bacteria. Diagn Microbiol Infect Dis 1993; 16(3):185-9.
27. Evans ME, Pollack M. Effect of antibiotic class and concentration on the release of lipopolysaccharide from *Escherichia coli.* J Infect Dis. 1993; 167(6):1336-43.
28. Crosby HA, Bion JF, Penn CW et al. Antibiotic-induced release of endotoxin from bacteria in vitro. J Med Microbiol 1994; 40(1):23-30.
29. Prins JM, Kuijper EJ, Mevissen ML et al. Release of tumor necrosis factor alpha and interleukin 6 during antibiotic killing of *Escherichia coli* in whole blood: influence of antibiotic class, antibiotic concentration, and presence of septic serum. Infect Immun 1995; 63(6):2236-42.
30. Lamp KC, Rybak MJ, McGrath BJ et al. Influence of antibiotic and E5 monoclonal immunoglobulin M interactions on endotoxin release from *Escherichia coli* and *Pseudomonas aeruginosa.* Antimicrob Agents Chemother 1996; 40(1):247-52.
31. Van Langevelde P, Van Dissel JT, Ravensberger E et al. Antibiotic-induced release of lipoteichoic acid and peptidoglycan from *Staphylococcus aureus:* quantitative measurements and biological reactivities. Antimicrob Agents Chemother 1998; 42(12):3073-8.
32. Trautmann M, Zick R, Rukavina T et al. Antibiotic-induced release of endotoxin: in-vitro comparison of meropenem and other antibiotics. J Antimicrob Chemother 1998; 41(2):163-9.
33. Sjolin J, Goscinski G, Lundholm M et al. Endotoxin release from *Escherichia coli* after exposure to tobramycin: dose-dependency and reduction in cefuroxime-induced endotoxin release. Clin Microbiol Infect 2000; 6(2):74-81.
34. Xu N, Yuan J, Xiao G et al. An experimental study on the release of endotoxin from gram negative bacteria induced by antibiotics. Zhonghua Shao Shang Za Zhi 2001; 17(2):75-9.
35. Bentley AP, Barton MH, Lee MD et al. Antimicrobial-induced endotoxin and cytokine activity in an in vitro model of septicemia in foals. Am J Vet Res 2002; 63(5):660-8.
36. Krehmeier U, Bardenheuer M, Voggenreiter G et al. Effects of antimicrobial agents on spontaneous and endotoxin-induced cytokine release of human peripheral blood mononuclear cells. J Infect Chemother 2002; 8(2):194-7.
37. Tsumura H, Hiyama E, Kodama T et al. Relevance of antimicrobial agent-induced endotoxin release from in vitro cultured *Escherichia coli* and in vivo experimental infection with Gram-negative bacilli. Int J Antimicrob Agents 2003; 21(5):463-70.
38. Goscinski G, Lundholm M, Odenholt I et al. Variation in the propensity to release endotoxin after cefuroxime exposure in different gram-negative bacteria: uniform and dose-dependent reduction by the addition of tobramycin. Scand J Infect Dis 2003; 35(1):40-6.
39. Tsuji M, Matsuda H, Miwa H et al. Antimicrobial-induced release of endotoxin from *Pseudomonas aeruginosa:* comparison of in vitro and animal models. J Antimicrob Chemother 2003; 51(2):353-9.
40. Dofferhoff AS, Nijland JH, De Vries-Hospers HG et al. Effects of different types and combinations of antimicrobial agents on endotoxin release from gram-negative bacteria: an in-vitro and in-vivo study. Scand J Infect Dis 1991; 23(6):745-54.
41. Arditi M, Kabat W, Yogev R. Antibiotic-induced bacterial killing stimulates tumor necrosis factor-alpha release in whole blood. J Infect Dis 1993; 167(1):240-4.
42. Dofferhoff AS, Esselink MT, De Vries-Hospers HG et al. The release of endotoxin from antibiotic-treated *Escherichia coli* and the production of tumour necrosis factor by human monocytes. J Antimicrob Chemother 1993; 31(3):373-84.
43. Yokochi T, Kusumi A, Kido N et al. Differential release of smooth-type lipopolysaccharide from *Pseudomonas aeruginosa* treated with carbapenem antibiotics and its relation to production of tumor necrosis factor alpha and nitric oxide. Antimicrob Agents Chemother 1996; 40(10):2410-2.
44. Inoue E, Komoto E, Taniyama Y et al. Antibacterial activity of sulopenem, a new parenteral penem antibiotic. Jpn J Antibiot 1996; 49(4):338-51.
45. Narita K, Koide N, Morikawa A et al. Differential release of endotoxin from *Pseudomonas aeruginosa* treated with beta-lactam antibiotics and its effect on the lethal activity. Jpn J Med Sci Biol 1997; 50(6):233-9.
46. Arditi M, Zhou J. Differential antibiotic-induced endotoxin release and interleukin-6 production by human umbilical vein endothelial cells (HUVECs): amplification of the response by coincubation of HUVECs and blood cells. J Infect Dis 1997; 175(5):1255-8.
47. Takahashi K, Narita K, Kato Y et al. Low-level release of Shiga-like toxin (verocytotoxin) and endotoxin from enterohemorrhagic *Escherichia coli* treated with imipenem. Antimicrob Agents Chemother 1997; 41(10):2295-6.
48. Van Langevelde P, Kwappenberg KM, Groeneveld PH, Mattie H, van Dissel JT. Antibiotic-induced lipopolysaccharide (LPS) release from *Salmonella typhi:* delay between killing by ceftazidime and imipenem and release of LPS. Antimicrob Agents Chemother 1998; 42(4):739-43.
49. Horii T, Kobayashi M, Sato K et al. An in-vitro study of carbapenem-induced morphological changes and endotoxin release in clinical isolates of gram-negative bacilli. J Antimicrob Chemother 1998; 41(4):435-42.
50. Trautmann M, Heinemann M, Zick R et al. Antibacterial activity of meropenem against *Pseudomonas aeruginosa,* including antibiotic-induced morphological changes and endotoxin-liberating effects. Eur J Clin Microbiol Infect Dis 1998; 17(11):754-60.
51. Yamaguchi S, Sato S, Toriya M et al. Effects of isepamicin and beta-lactam antibiotics on the release of endotoxin from *Pseudomonas aeruginosa.* Jpn J Antibiot 1999; 52(1):41-56.
52. Trautmann M, Heinemann M, Moricke A et al. Endotoxin release due to ciprofloxacin measured by three different methods. J Chemother 1999; 11(4):248-54.
53. Horii T, Ichiyama S, Ohta M et al. Relationship between morphological changes and endotoxin release induced by carbapenems in *Pseudomonas aeruginosa.* J Med Microbiol. 1999; 48(3):309-15.
54. Cui W, Morrison DC, Silverstein R. Differential tumor necrosis factor alpha expression and release from peritoneal mouse macrophages in vitro in response to proliferating gram-positive versus gram-negative bacteria. Infect Immun 2000; 68(8):4422-9.

55. Bucklin SE, Fujihara Y, Leeson MC et al. Differential antibiotic-induced release of endotoxin from gram-negative bacteria. Eur J Clin Microbiol Infect Dis 1994; 13 Suppl 1:S43-51.
56. Leeson MC, Fujihara Y, Morrison DC. Evidence for lipopolysaccharide as the predominant proinflammatory mediator in supernatants of antibiotic-treated bacteria. Infect Immun. 1994; 62(11):4975-80.
57. Kishi K, Hirai K, Hiramatsu K et al. Clindamycin suppresses endotoxin released by ceftazidime-treated *Escherichia coli* 055:B5 and subsequent production of tumor necrosis factor alpha and interleukin-1 beta. Antimicrob Agents Chemother 1999; 43(3):616-622.
58. Horii T, Kimura T, Nadai M et al. Lincomycin-induced endotoxin release in *Escherichia coli* sepsis: evidence for release in vitro and in vivo. Int J Infect Dis 2000; 4(3):118-122.
59. Liang AH, Xue BY, Liang RX et al. Inhibitory effect of egg white lysozyme on ceftazidime-induced release of endotoxin from *Pseudomonas aeruginosa*. Xue Xue Bao 2003; 38(11):801-4.
60. Khair OA, Devalia JL, Abdelaziz MM et al. Effect of erythromycin on *Haemophilus influenzae* endotoxin-induced release of IL-6, IL-8 and sICAM-1 by cultured human bronchial epithelial cells. Eur Respir J 1995; 8(9):1451-7.
61. Orman KL, English BK. Effects of antibiotic class on the macrophage inflammatory response to *Streptococcus pneumoniae*. J Infect Dis 2000; 182(5):1561-1565.
62. Gerber J, Pohl K, Sander V, Bunkowski S et al. Rifampin followed by ceftriaxone for experimental meningitis decreases lipoteichoic acid concentrations in cerebrospinal fluid and reduces neuronal damage in comparison to ceftriaxone alone. Antimicrob Agents Chemother 2003; 47(4):1313-7.
63. Shenep JL, Mogan KA. Kinetics of endotoxin release during antibiotic therapy for experimental gram-negative bacterial sepsis. J Infect Dis 1984; 150(3):380-8.
64. Walterspiel JN, Kaplan SL, Mason EO Jr. Protective effect of subinhibitory polymyxin B alone and in combination with ampicillin for overwhelming *Haemophilus influenzae* type B infection in the infant rat: evidence for in vivo and in vitro release of free endotoxin after ampicillin treatment. Pediatr Res 1986; 20(3):237-41.
65. Johnston CA, Greisman SE. Endotoxemia induced by antibiotic therapy: a mechanism for adrenal corticosteroid protection in gram-negative sepsis. Trans Assoc Am Physicians 1984; 97:172-81.
66. Rogers MJ, Moore R, Cohen J. The relationship between faecal endotoxin and faecal microflora of the C57BL mouse. J Hyg (Lond) 1985; 95(2):397-402.
67. Goris H, De Boer F, Van der Waaij D. Oral administration of antibiotics and intestinal flora associated endotoxin in mice. Scand J Infect Dis 1986; 18(1):55-63.
68. Van Leeuwen PA, Hong RW, Rounds JD et al. Hepatic failure and coma after liver resection is reversed by manipulation of gut contents: the role of endotoxin. Surgery 1991; 110(2):169-74.
69. Stockwell JA, Huang YC, Su YF et al. Bactericidal antibiotics increase tumor necrosis factor-alpha and cardiac output in rats after cecal ligation and puncture. Circ Shock 1994; 42(2):68-75.
70. Anderson R, Fernandes AC, Eftychis HE. Studies on the effects of ingestion of a single 500 mg oral dose of erythromycin stearate on leucocyte motility and transformation and on release in vitro of prostaglandin E2 by stimulated leucocytes. J Antimicrob Chemother 1984; 14(1):41-50.
71. Nitsche D, Schulze C, Oesser S et al. Impact of different classes antimicrobial agents on plasma endotoxin activity. Arch Surg 1996; 131(2):192-9.
72. Rosman C, Westerveld GJ, Van Oeveren W et al. Effect of intraperitoneal antimicrobials on the concentration of bacteria, endotoxin, and tumor necrosis factor in abdominal fluid and plasma in rats. Eur Surg Res 1996; 28(5):351-60.
73. Yokochi T, Narita K, Morikawa A et al. Morphological change in *Pseudomonas aeruginosa* following antibiotic treatment of experimental infection in mice and its relation to susceptibility to phagocytosis and to release of endotoxin. Antimicrob Agents Chemother 2000; 44(1):205-6.
74. Wang S, Wu B, Huang F. An experimental study of antibiotic - induced endotoxin release in *Pseudomonas aeruginosa* bacteremia inburned rats. Zhonghua Shao Shang Za Zhi 2000; 16(2):93-5.
75. Rotimi VO, Al-Sweih NN, Anim JT et al. Influence of in-vivo endotoxin liberation on antib-anaerobic antimicrobial efficacy. J Chemother 2001; 13(5):510-8.
76. Xu N, Yuan J, Xiao G et al. An experimental study of the LPS release from gram-negative bacteria induced by antibiotics (Part two). Zhonghua Shao Shang Za Zhi 2002; 18(2):92-4.
77. Vianna RC, Gomes RN, Bozza FA et al. Antibiotic treatment in a murine model of sepsis: impact on cytokines and endotoxin release. Shock 2004; 21(2):115-20.
78. Friedland IR, Jafari H, Ehrett S et al. Comparison of endotoxin release by different antimicrobial agents and the effect on inflammation in experimental *Escherichia coli* meningitis. J Infect Dis 1993; 168(3):657-62.
79. Jauris-Heipke S, Leake ER, Billy JM et al. The effect of antibiotic treatment on the release of endotoxin during nontypable Haemophilus influenzae-induced otitis media in the chinchilla. Acta Otolaryngol 1997; 117(1):109-12.
80. Bottcher T, Ren H, Goiny M et al. Clindamycin is neuroprotective in experimental *Streptococcus pneumoniae* meningitis compared with ceftriaxone. J Neurochem 2004; 91(6):1450-60.
81. D'Agostino P, La Rosa M, Barbera C et al. Doxycycline reduces mortality to lethal endotoxemia by reducing nitric oxide synthesis via an interleukin-10-independent mechanism. J Infect Dis 1998; 177(2):489-92.
82. Carney DE, Lutz CJ, Picone AL et al. Matrix metalloproteinase inhibitor prevents acute lung injury after cardiopulmonary bypass. Circulation 1999; 27;100(4):400-6.
83. Lalu MM, Gao CQ, Schulz R. Matrix metalloproteinase inhibitors attenuate endotoxemia induced cardiac dysfunction: a potential role for MMP-9. Mol Cell Biochem 2003; 251(1-2):61-6.
84. Opal SM, Palardy JE, Parejo N et al. Lipopolyamines as a therapeutic strategy in experimental Gram-negative bacterial sepsis. J Endotoxin Res 2001; 7(1):35-8.
85. Lin Y, Leach WJ, Ammons WS. Synergistic effect of a recombinant N-terminal fragment of bactericidal/permeability-increasing protein and cefamandole in treatment of rabbit gram-

negative sepsis. Antimicrob Agents Chemother 1996; 40(1):65-9.
86. Hirata N, Hiramatsu K, Kishi K et al. Pretreatment of mice with clindamycin improves survival of endotoxin shock by modulating the release of inflammatory cytokines. Antimicrob Agents Chemother 2001; 45(9):2638-42.
87. Bucklin SE, Morrison DC. Bacteremia versus endotoxemia in experimental mouse leukopenia--role of antibiotic chemotherapy. J Infect Dis 1996; 174(6):1249-54.
88. Teklu B, Habte-Michael A, Warrell DA et al. Meptazinol diminishes the Jarisch-Herxheimer reaction of relapsing fever. Lancet. 1983; 1(8329):835-9.
89. Arditi M, Ables L, Yogev R. Cerebrospinal fluid endotoxin levels in children with *H. influenzae* meningitis before and after administration of intravenous ceftriaxone. J Infect Dis 1989; 160(6):1005-11.
90. Mustafa MM, Mertsola J, Ramilo O et al. Increased endotoxin and interleukin-1 beta concentrations in cerebrospinal fluid of infants with coliform meningitis and ventriculitis associated with intraventricular gentamicin therapy. J Infect Dis 1989; 160(5):891-5.
91. Prins JM, Van Agtmael MA, Kuijper EJ et al. Antibiotic-induced endotoxin release in patients with gram-negative urosepsis: a double-blind study comparing imipenem and ceftazidime. J Infect Dis 1995; 172(3):886-91.
92. Giamarellou-Bourboulis EJ, Perdios J et al. Impact of cefuroxime administration on endotoxin (LPS) and tumour necrosis factor-alpha (TNFalpha) blood levels in patients suffering from acute pyelonephritis: a preliminary report. Int J Antimicrob Agents 1999; 11(2):115-9.
93. Luchi M, Morrison DC, Opal S et al. A comparative trial of imipenem versus ceftazidime in the release of endotoxin and cytokine generation in patients with gram-negative urosepsis. Urosepsis Study Group. J Endotoxin Res 2000; 6(1):25-31.
94. Holzheimer RG, Hirte JF, Engelhardt W et al. Different endotoxin release and IL-6 plasma levels after antibiotic administration in surgical intensive care patients. J Endotoxin Res 1996; 3(3):261-267.
95. Ishikawa M, Miyauchi T, Yagi K et al. Clinical relevance of antibiotic-indueced endotoxin release in patients undergoing hepatic resection. World J Surg 1999; 23(1):75-79.
96. Byl B, Clevenbergh P, Kentos A et al. Ceftazidime- and imipenem-induced endotoxin release during treatment of gram-negative infections. Eur J Clin Microbiol Infect Dis 2001; 20(11):804-7.
97. Maskin B, Fontan PA, Spinedi EG et al. Evaluation of endotoxin release and cytokine production induced by antibiotics in patients with Gram-negative nosocomial pneumonia. Crit Care Med 2002; 30(2):349-54.
98. Holzheimer RG. Oral antibiotic prophylaxis can influence the inflammatory response in aortic aneurysm repair: results of a randomized clinical study. J Chemother 2003; 15(2):157-64.
99. Simpson AJ, Opal SM, Angus BJ et al. Differential antibiotic-induced endotoxin release in severe melioidosis. J Infect Dis 2000; 181(3):1014-9.
100. Wang HM, Cao WF, Peng YZ et al. Changes in plasma levels of LPS, TNFalpha and IL-6 in burn patients with severe infection treated with imipenem or cefoperazone. Zhonghua Shao Shang Za Zhi 2004; 20(2):95-7.
101. Jaber BL. Pyrogenic reactions following gentamicin therapy: an alternative explanation. Med Hypotheses 2001; 57(6):727-8.

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