Pharmacodynamics of antibiotics with respect to bacterial killing of and release of lipoteichoic acid by *Streptococcus pneumoniae*

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Objectives: There are marked differences in the amount of immunoreactive components such as lipoteichoic acid (LTA) released from Gram-positive bacteria following exposure to different antibiotics. Little is known about the kinetics and amount of release of such components in relation to bacterial killing.

Methods: Bacterial killing and LTA release from *Streptococcus pneumoniae* type 3 during exposure to ceftriaxone, meropenem, rifampicin, rifabutin, quinupristin/dalfopristin, and trovafloxacin in tryptic soy broth were quantified microbiologically and by ELISA, respectively. We applied a mathematical model to characterize quantitatively the amount of lipoteichoic acid released and the statistical moments of this release.

Results: The model approach revealed that (i) the lag time to release of LTA was very similar for individually killed bacterial cells (~120 min), whatever the killing mechanism effected by the antibiotic, and (ii) the amount of LTA released per killed bacterial cell, a value that we regard as an indicator of the relation between antibacterial efficacy and possible adverse immunostimulatory effects due to release of cell wall components, differs markedly between antibiotics, even at antibiotic concentrations inducing equal killing. Rifamycins were most effective in killing *S. pneumoniae* while causing the least LTA release per killed bacterial cell; the amount released was about one-half that by quinupristin–dalfopristin and trovafloxacin, and one-quarter that by ceftriaxone and meropenem.

Conclusions: In the evaluation of antibacterial drugs, the present model provides useful information on the whole process of bacterial killing and release of immunoreactive components from the bacterial cell wall.

Keywords: *S. pneumoniae*, LTA, immunostimulatory components

Introduction

It has been suggested that antibiotic-induced release of immunostimulatory components like lipopolysaccharide and lipoteichoic acid from the bacterial cell wall may contribute to the development of sepsis and septic shock and inflammatory complications in patients treated for severe infection.¹,² These components are released after bacteriolysis that occurs when microbial multiplication is interrupted following activation of autolytic cell-wall breaking enzymes. While bacteriolysis may occur at a low level during bacterial replication, a more pronounced breakdown of the bacterial cell wall follows exposure to antibiotics. When lysis of bacteria occurs in vivo, immunostimulatory components are released. These agents can act on macrophages and induce a cascade of pro-inflammatory reactions in the host. For instance, in animal models of *Escherichia coli* peritonitis and of *Streptococcus pneumoniae* meningitis, the release of immunostimulatory components of the bacterial cell wall was associated with mortality.¹,² In the latter model, morbidity and mortality have been attributed to the inflammatory response within the subarachnoid space to bacterial products liberated following antibiotic-induced lysis of bacteria.³,⁴ Such findings led to many studies that addressed the issue of whether the consequences of the inflammatory response due to bacterial components could be attenuated with immunomodulatory drugs. In a recent clinical study, the proportion of patients with bacterial meningitis who had an unfavourable outcome was reduced when given adjunctive treatment with dexamethasone.⁵ Less attention has been given to possible differences between various kinds of antibiotics as to the amount of immunostimulatory...
components such as lipopolysaccharide and lipoteichoic acid released. Because some antibiotics, in addition to bacterial killing, can induce filament formation whereas others induce rapid cell lysis after spheroplast formation, antibiotics at concentrations inducing equivalent killing of the bacterial inoculum may differ considerably in the total amount of immunostimulatory components released and the kinetics of this release. Such differences might prove clinically relevant in many conditions including bacterial meningitis mentioned above, or, for instance, in Gram-negative bacteremia, in which the presence in the blood of free lipopolysaccharide rather than of intact microorganisms is associated with in-hospital mortality.

In previous papers, we described the release of lipoteichoic acid by Gram-positive microorganisms in the presence of antibiotics. Since then, we have developed a mathematical model to characterize this release more quantitatively by various pharmacodynamic parameters, and in relation to bacterial killing. Here, we examined not only the total amount released, but used statistical moments to characterize this release further.

**Methods**

**Release of lipoteichoic acid and teichoic acid**

The release of lipoteichoic acid (LTA) and teichoic acid (TA) from a *Streptococcus pneumoniae* type 3 strain during exposure to various concentrations of ceftriaxone, meropenem, rifampicin, rifabutin, quinupristin/dalfopristin, and trovafloxacin in tryptic soy broth were quantified by enzyme immunoassay, as described previously. In short, the assay uses the mouse immunoglobulin A monoclonal antibody TEPC-15 (Sigma, Deisenhofen, Germany), which recognizes the phosphorylcholine residues of LTA and TA, as the capture antibody; a polyclonal rabbit antiserum was used as the detector antibody. Bound rabbit antibodies were quantified with peroxidase-conjugated goat-anti-rabbit IgG antibodies. Purified LTA from *S. pneumoniae* served for the construction of the standard curve.

In the same experiment, bacterial densities were determined by plating 10 μL samples of 10-fold dilutions of bacteria onto blood agar plates.

**Model**

The release of LTA was characterized by three pharmacodynamic parameters:

(i) The total amount of lipoteichoic acid released (LTA_total).

(ii) The mean duration of time for the release of lipoteichoic acid from the start of exposure to antibiotics (MRT).

(iii) The standard deviation of the MRT (SDMRT).

The LTA_total was calculated as follows. First, since LTA is stable, it was assumed that the cumulative amount of released LTA should increase in time until time $T$, when the release is complete. Therefore, if the observed concentration seemed to decrease in time, this was considered to be due to analytical inaccuracy and not to real disappearance of LTA. Thus, the highest concentration was considered equal to the final concentration [see Figure 1(b) for an example]. From this plot, statistical moments were calculated.

**Statistical moments**

Statistical moments are based on the probability distribution of an event. If the probability function is defined as $p(t)$, then by definition $\int_0^\infty p(t)dt = 1$. The $n$th statistical moment is defined as $\int_0^\infty t^n p(t)dt$.

LTA is released in a finite time $T$. Let the probability function for the release time be defined as $f(t)$, where $F_T = \int_0^T f(t)dt = 1$. The function of the amount of LTA released during exposure to the antibiotic up to a given time $t$ (i.e. the corrected plot in Figure 1b) is called $F(t)$. The first derivative of the latter function is proportional to the probability function $f(t)$, and the proportionality factor is LTA_total. Thus, $F'(t) = LTA_{total} \int_0^t f(t)dt$. According to Brockmeyer, the $n$th statistical moment is equal to $\int_0^\infty t^n f(t)dt$ and the area under the curve of the probability function from time $t$ to time $T$, is called the prospective area under the curve at time $t$ (PAUAC). From the above, it follows that the plot of $[LTA_{total} - F(t)]/LTA_{total}$ is equal to PAUAC. Estimated values of this plot were calculated as the difference between the maximum corrected value of released LTA and the corrected value at time $t$. Using the algorithm of Brockmeyer, PAUC1 and PAUC2 were calculated by the trapezoid method. It should be noted that this is a slight modification of the algorithm by Brockmeyer. The original algorithm is based on the assumption that the plot of measured values is proportional to the probability distribution. This is only so in the case of exponential decline, as for instance in the case of clearance of a drug from the plasma. The respective statistical moments $M_1$ and $M_2$ are the values of PAUC1 and 2.PAUC2 at time $t = 0$ (see the Brockmeyer equation). The MRT is equal to $M_1$ and the SDMRT is $\sqrt{M_2 - M_1}$. Figure 1(b) also shows the calculated MRT (=5.47 h) and the SDMRT (=2.33 h).

LTA is released from killed bacterial cells (defined as microorganisms unable to grow in 18–24 h when plated on solid culture media). Therefore, the time course of the number of killed cells was calculated...
as well, to arrive at values for the total number of killed cells, the mean duration of time of this killing (MKT) and its standard deviation (SDMKT). The number of killed cells (Nk) was estimated as follows. First, it was assumed that bacterial cells either die, or propagate at the same exponential rate as the controls. This means that upon incubation of microorganisms with an increasing concentration of an antibiotic, bacterial killing is presumed to occur independently of any remaining bacterial proliferation at such an antibiotic concentration. In other words, bacterial cells that are not dying through antibiotic action are presumed to be growing at the same rate as untreated controls. At least in the case of β-lactam antibiotics, there is experimental proof for this assertion. The assumption may not be correct, however, for inhibitors of bacterial protein synthesis.

Thus, the number of dead cells that are produced is proportional to the number of viable cells:

$$\frac{dN_k}{dt} = r_k \cdot N$$

in which $r_k$ is the real exponential killing rate and $N$ the actual number of microorganisms. The killing rate $r_k$ is $r_c - r$, in which $r_c$ is the exponential growth rate of the control and $r$ is the actual exponential change of $N$. For each time interval, the number of viable cells $N$ is defined as:

$$N_i = N_i \cdot e^{r_i}$$

in which $N_i$ is the initial value of $N$ for this time interval. For each time interval, this leads to the following equation:

$$N_k = \left[\frac{(r_c - r)}{r}\right] \cdot N_i \cdot (e^{r_i} - 1)$$

Values of $r_c$ and $r$ were calculated separately for each time interval from the numbers in the corrected control and those in the presence of the antibiotic. The cumulative plot of the values of $N_k$ is the plot for the ‘production of killed cells’ (Figures 1a and 2). As a result of experimental error as well as the spontaneous decrease in numbers sometimes seen in the controls at the end of the experiment, this procedure might lead to negative values of $N_k$. Therefore, the highest cumulative count was considered equal to the final count (Figure 1a). This plot was used as the basis for the calculation of the statistical moments, as described above for LTA ($F(t)$). In the example, the MKT was 2.37 h and the SDMKT 2.03 h. It should be noted that the lowest possible estimate of the MKT is 1.5 h, since the first sampling time was after 3 h of exposure.

The difference between the MRT of LTA and the MKT of the microorganism was calculated as a distinct pharmacodynamic parameter for a particular antibiotic (compare Figure 1a and b). In the example, this delay time is 2.92 h. Furthermore, the rate of killing may be expected to be similar to the rate of LTA release. Therefore, the standard deviations of the two parameters should also be similar. In the example, this difference between SDMRT and SDMKT is 0.21 h. Finally, to relate bacterial killing to LTA release, the total amount of released LTA was divided by the total number of killed cells to obtain the amount of LTA per killed cell. In the example, this amounted to 245 ng per $10^6$ killed bacterial cells.

For each parameter, the results of the lower and the higher range concentrations were analysed separately by analysis of variance, with the three experiments per concentration as categorical variables and the concentrations as linear and non-linear regression.

**Results**

**Release of lipoteichoic acid and teichoic acid**

The data concerning the release of LTA and TA were published previously. In short, after 3–12 h of incubation with the various antibiotics, the LTA and TA concentrations were lowest after exposure to rifampicin and rifabutin, and intermediate after exposure to quinupristin–dalfopristin and trovafloxacin, compared with the amount released after exposure to ceftriaxone. These data were used in the calculations. For the various antibiotics, the total amount of released LTA (LTA$\text{total}$) is shown in Table 1. The mean release time of LTA (MRT), and its standard deviation (SDMRT), and the mean killing time (MKT) and its standard deviation (SDMKT) are shown in Table 2. The relation between LTA$\text{total}$ and the number of killed cells is shown in Figure 3. The results of the calculations for the various antibiotics may be summarized as follows.

**Ceftriaxone.** LTA$\text{total}$ in the presence of ceftriaxone decreased with increasing concentration; in the higher concentration range, this concentration dependency was significant ($P < 0.0001$). LTA release levelled off at about 2000 μg/L. The MRT and SDMRT also decreased in a concentration-dependent way; in the higher concentration range, this was significant ($P = 0.002$ and $P = 0.043$, respectively). Only at the lowest concentration were the calculated values of the MRT well above the lowest possible estimate of 1.5 h. The difference between MRT and MKT was not dose-dependent in a significant way; at the low concentration range it was about 2 h. The SDMRT and the SDMKT were not significantly different, indicating similar rates of killing and LTA release. Finally, the amount of LTA$\text{total}$ per million killed cells decreased in a dose-dependent way in the higher concentration range ($P < 0.0001$), levelling off at 11 ng. However, there appears to be a discrepancy between the results in the lower concentration and the higher concentration range, possibly due to experimental reasons (e.g. inter-day variation).

**Meropenem.** In the presence of meropenem, LTA$\text{total}$ decreased in a dose-dependent way; in the lower ($P = 0.049$) as well as in the higher concentration range ($P < 0.0001$). Release levelled off at about the same level as ceftriaxone. The MRT also decreased in a concentration-dependent way; in the higher concentration range, this concentration dependency was significant ($P = 0.017$). The SDMRT was not concentration-dependent; its mean value amounted to 2.77 h. At no concentration was the MRT much above the lowest possible estimate of 1.5 h. The difference between MRT and MKT

![Figure 2](image-url)
Bacterial killing and LTA release from *S. pneumoniae* during exposure to antibiotics

Table 1. Release of lipoteichoic acid (µg/L) by *Streptococcus pneumoniae* in the presence of antibiotics

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>0</th>
<th>0.008</th>
<th>0.015</th>
<th>0.031</th>
<th>0.063</th>
<th>0.125</th>
<th>0.50</th>
<th>2.0</th>
</tr>
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<tr>
<td>None</td>
<td>3427</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>9979</td>
<td>12 570</td>
<td>10 348</td>
<td>8238</td>
<td>5275</td>
<td>2367</td>
<td>2161</td>
<td></td>
</tr>
<tr>
<td>Meropenem</td>
<td>7834</td>
<td>9612</td>
<td>5205</td>
<td>3868</td>
<td>2999</td>
<td>2302</td>
<td>2095</td>
<td></td>
</tr>
<tr>
<td>Trovafloxacin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11 534</td>
<td>14 400</td>
<td>7565</td>
<td>1499</td>
</tr>
<tr>
<td>Quinupristin/dalfopristin</td>
<td>4059</td>
<td>5061</td>
<td>2700</td>
<td>652</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampicin</td>
<td>3806</td>
<td>5197</td>
<td>6664</td>
<td>3508</td>
<td>1208</td>
<td>542</td>
<td>536</td>
<td></td>
</tr>
<tr>
<td>Rifabutin</td>
<td>10 426</td>
<td>447</td>
<td>239</td>
<td>506</td>
<td>587</td>
<td>590</td>
<td>630</td>
<td></td>
</tr>
</tbody>
</table>

Each value is the mean of three separate experiments (after Ref. 7).

Table 2. Mean release time (MRT, h) of lipoteichoic acid, standard deviation of MRT (SDMRT), mean killing time (MKT) of *Streptococcus pneumoniae* and standard deviation of MKT (SDMKT) in the presence of antibiotics

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MRT</th>
<th>SDMRT</th>
<th>MKT</th>
<th>SDMKT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ceftriaxone</td>
<td>3.87 ± 1.19</td>
<td>2.34 ± 0.71</td>
<td>1.69 ± 0.29</td>
<td>1.61 ± 0.08</td>
</tr>
<tr>
<td>Meropenem</td>
<td>3.43 ± 0.86</td>
<td>2.77 ± 0.49</td>
<td>1.57 ± 0.10</td>
<td>1.53 ± 0.03</td>
</tr>
<tr>
<td>Trovafloxacin</td>
<td>4.84 ± 0.84</td>
<td>2.37 ± 0.26</td>
<td>2.81 ± 1.42</td>
<td>1.60 ± 0.05</td>
</tr>
<tr>
<td>Quinupristin/dalfopristin</td>
<td>5.33 ± 0.96</td>
<td>2.69 ± 0.27</td>
<td>1.86 ± 0.45</td>
<td>1.75 ± 0.28</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>5.26 ± 0.73</td>
<td>2.58 ± 0.40</td>
<td>1.83 ± 0.21</td>
<td>3.01 ± 1.42</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>4.62 ± 0.69</td>
<td>3.10 ± 0.37</td>
<td>1.71 ± 0.15</td>
<td>1.69 ± 0.11</td>
</tr>
</tbody>
</table>

Each value is the mean (± SD) of three estimates concerning the three separate experiments.

![Figure 3](image_url)

Figure 3. Amount of lipoteichoic acid released by 10⁶ killed cells of *Streptococcus pneumoniae* in the presence of the antibiotics ceftriaxone (open circles), meropenem (filled circles), trovafloxacin (open triangles), quinupristin/dalfopristin (filled triangles), rifampicin (open squares) and rifabutin (filled squares). Lines represent separate experiments, and connect values that are the mean of three independent determinations.

was not dose-dependent in a significant way; its mean value was 2.1 h. The mean SDMRT was somewhat (i.e. 1.22 h), but significantly, longer than the SDMKT (*P* < 0.05). The amount of LTA<sub>total</sub> per million killed cells decreased in a dose-dependent way in the higher concentration range (*P* < 0.002), levelling off at 7 ng. Here too, there was a discrepancy between the results in the lower concentration and the higher concentration range.

*Trovafloxacin.* LTA<sub>total</sub> in the presence of trovafloxacin decreased in a concentration-dependent way (*P* < 0.0001). At the highest concentration, it still did not level off at a value of 1499 µg/L. The MRT decreased in a dose-dependent way, but not significantly so (*P* = 0.066). The SDMRT was not concentration-dependent; its mean value was 2.37 h. The MKT also decreased with increasing concentration but this was not significant (*P* = 0.15). The difference between MRT and MKT was not concentration-dependent in a significant way, its mean value was 2.0 h. The mean SDMRT was only 0.5 h longer than the SDMKT and this difference is not significant, indicating similar rates of killing and LTA release.

*Quinupristin/dalfopristin.* LTA release decreased in a dose-dependent way (*P* = 0.027). At the highest concentration, it still did not level off at a value of 675 µg/L. The MRT decreased in a dose-dependent way (*P* < 0.0001). The SDMRT was not concentration-dependent; its mean value was 2.69 h. The MKT could only be evaluated at the highest two concentrations, since at the lower concentrations there was no effect at all on the number of microorganisms. In that concentration range, the MKT decreased (*P* = 0.005). The difference between MRT and MKT was somewhat concentration-dependent, but not significantly so (*P* = 0.073), its mean value was 2.8 h. The mean SDMRT was 0.8 h longer than the SDMKT (*P* < 0.05). LTA<sub>total</sub> per million killed bacterial cells was not concentration-dependent, the mean value being 6 ng.

*Rifampicin.* In the presence of rifampicin, LTA<sub>total</sub> decreased with increasing concentrations only in the high concentration range (*P* < 0.0001). The release levelled off at about 540 µg/L. Similarly, the
MRT decreased in a dose-dependent way in the higher concentration range ($P = 0.025$). The SD$_{MRT}$ was not concentration-dependent; its mean value was 2.58 h. The MKT was also not concentration-dependent; its mean value was 1.83 h. The difference between MRT and MKT was not dose-dependent in a significant way; its mean value was 3.4 h. The SD$_{MRT}$ and SD$_{MKT}$ were not significantly different, indicating similar rates of bacterial killing and LTA release. LTA$_{total}$ per million killed bacterial cells decreased in a dose-dependent fashion in the higher concentration range ($P = 0.015$), levelling off at 2 ng.

Rifabutin. In the presence of rifabutin, LTA$_{total}$ decreased with increasing concentrations in the lower and higher concentration range ($P < 0.0001$ and $P = 0.037$, respectively). However, there was a discrepancy between the two series of experiments: the lowest values in the lower range were about 230 µg/L, and in the higher range they were 600 µg/L. The MRT did not decrease. The SD$_{MRT}$ was not concentration-dependent; its mean value was 3.13 h. The MKT decreased only in the lower concentration range ($P = 0.007$). The difference between MRT and MKT was not dose-dependent in a significant way; its mean value was 3.2 h. The mean SD$_{MRT}$ was 1.44 h longer than the SD$_{MKT}$ ($P < 0.05$). The discrepancy between the two concentration ranges was also seen in the amount of LTA released per million bacterial cells: the lowest value in the lower range was less than 1 ng and in the highest range, it was about 2 ng.

Discussion

The main finding of this study which employed a mathematical model to analyse the whole process of bacterial killing and release of cell wall components is that antibiotics with different modes of action differ markedly in the release of lipoteichoic acid per killed bacterial cell, a value that we regard as an indicator of the relation between antibacterial efficacy and possible adverse immunostimulatory effects due to release of cell wall components. Moreover, this amount of LTA released per killed bacterial cell differs between antibiotics even at antibiotic concentrations inducing equal killing. Overall, rifamycins were most effective in killing *S. pneumoniae* while causing the least LTA release per killed bacterial cell: the amount of LTA released by rifamycins was about one-half that by quinupristin–dalfopristin and trovafloxacin, and about one-quarter that by ceftriaxone and meropenem. The model approach further revealed that in *S. pneumoniae*, the lag time to release of LTA was very similar for individually killed bacterial cells (i.e. about 120 min), whichever the killing mechanism of the antibiotic.

The conclusions derived depend on the validity and assumptions inherent in the mathematical model. For instance, part of the differences between antibiotic-induced LTA release may be due to the assumption that in the presence of antibiotics, proliferation proceeds at a normal rate, while killing proceeds independently. This assumption may be valid for β-lactam antibiotics like ceftriaxone and meropenem, but not, for instance, rifamycins. Thus, if at a given concentration the net number of bacteria neither increases nor decreases over time, this implies for a β-lactam that the killing rate is equal to the growth rate of the control. The rifamycins as RNA inhibitors hamper protein synthesis in a lethal way and probably at a sufficiently high concentration the number of cells that are killed is never more than that in the inoculum. As a result, the number of killed bacterial cells will be larger in the case of the β-lactam antibiotics, to obtain the same net result on numbers of microorganisms as in the case of the rifamycins. Unfortunately, at present there is a lack of detailed information on this subject so we had no certain way to adjust for such an effect, if indeed shown to be relevant, and had to apply the model in the same way for all antibiotics. If the assumption would be proven incorrect, however, it would lead to some overestimation of the total number of killed bacterial cells, an effect that is, on the whole, of influence most at lower antibiotic concentrations. In this respect, it should also be noted that in comparison with clinically therapeutic concentrations, the higher concentration range in our experiments seems more relevant than the lower range.

In the case of the β-lactams, the release of LTA occurs somewhat earlier than for the other antibiotics, but on no occasions immediately, the lowest value for the MRT being between 2 and 5 h. Again, this time of release is related to the time of killing. In this respect, there is not much difference between the antibiotics since the delay between killing and LTA release is 2–3 h for all antibiotics. The similarity between the standard deviations of the MRT and MKT occurring in most experiments indicate indeed that for individual killed bacterial cells, the lag time to release of LTA is very similar, whatever the killing mechanism.

The present analysis confirms that the amount of lipoteichoic acid released from *S. pneumoniae* upon antibiotic exposure differs between different kinds of antibiotics. Pharmacodynamic analysis showed that a great part of this variation is due to the difference in antibacterial efficacy, even at antibiotic concentrations inducing equal killing. Not only is there a distinct concentration dependency of LTA release, but for some antibiotics the effect levels off at the higher, clinically relevant concentrations. The difference in antibacterial efficacy and LTA release is illustrated best by the calculation of the release of lipoteichoic acid per killed bacterial cell, a value that we regard as a useful indicator of the relation between antibacterial efficacy and possible adverse immunostimulatory effects due to release of cell wall components. Of note, this value is much less concentration-dependent, but is still widely different between antibiotics. Per killed bacterial cell, the amount of LTA released by rifamycins was about one-half that by quinupristin/dalfopristin and trovafloxacin, and about one-quarter that for ceftriaxone and meropenem. Apparently, the similarity between the mode of action of ceftriaxone and meropenem is more important than the difference resulting in filament or spheroplast formation. Whatever the reason, the conclusion must be that the rifamycins are the most effective in killing *S. pneumoniae* while causing the least induction of lipoteichoic acid release. We did not measure the release of LTA in relation to serotype of pneumococcus. Therefore, we cannot exclude the possibility that the results might differ depending on the size of capsules.

In infection, bacterial components like lipoteichoic and teichoic acids can induce or enhance the inflammatory response of the host, an effect mediated by Toll-like receptor 2. We regard the differences between antibiotics in the release of lipoteichoic acid per killed bacterial cell as a relevant indicator of the relation between antibacterial efficacy and possible adverse immunostimulatory effects due to release of cell wall components. In this respect, the rifamycins are most effective in killing microorganisms while causing the least induction of lipoteichoic acid release. This interpretation is in line with experimental infection models, including an animal model of pneumococcal meningitis, in which rifamycins gave smaller increases of the concentrations of the pro-inflammatory components lipoteichoic and teichoic acids in the cerebrospinal fluid than did treatment with ceftriaxone. Similarly, at high doses, rifabutin was nearly as active as ceftriaxone.
Bacterial killing and LTA release from S. pneumoniae during exposure to antibiotics

in sterilizing the cerebrospinal fluid, whereas TNF-α activities in cerebrospinal fluid were lower with rifabutin than with ceftriaxone. Rifampicin reduced the mortality in experimental S. pneumoniae meningitis compared with ceftriaxone. Also, initiation of therapy with rifampicin and continuation of antibacterial therapy with a combination that includes a β-lactam like ceftriaxone appeared to decrease neuronal injury in experimental pneumococcal meningitis. Thus, it appears that sufficient evidence in support of modulating the release of pro-inflammatory bacterial cell wall components by specific choice of antibacterial agent has been gathered to support clinical trials in patients with Gram-positive infection. Such studies might focus on the clinical consequences of the inverse pharmacodynamic relation between dose of β-lactams and release of LTA, and on the use of rifamycins in combination therapies with β-lactams. In this respect, we feel that the pharmacodynamic parameters MRT, MKT and their standard deviations, apart from the total amount of LTA released will be of use in the evaluation of antibacterials as they provide succinct information on the whole process of bacterial killing and release of pro-inflammatory bacterial cell wall components.

References