Introduction

Most models of Streptococcus pneumoniae lobar pneumonia in immunocompetent rats or mice described in the literature\(^1\)\(^-\)\(^3\) result in either a fatal acute or a subacute infection characterized by a lobar consolidation, pleurisy and septicaemia. Although these infection models closely mimic the pathological patterns associated with pneumococcal pneumonia in man, most of them have a very high fatality rate. This is in contrast to human lung infection,\(^4\) where the overall case fatality rate is approximately 20–25% when the pneumonia is accompanied by bacteraemia.\(^5\) The recent emergence of S. pneumoniae strains with intermediate (MIC 0.1–1 mg/L) or high (MIC ≥ 2 mg/L) resistance to penicillin G has added a further challenge to the development of experimental models, since these isolates are of low virulence in rodents.\(^6\) To produce pneumonia caused by a pencillin-resistant (pen-R) strain, animals with impaired immunological defences are used.\(^7\)\(^-\)\(^9\)

The goal of this study was to develop a rat model of pneumococcal pneumonia caused by a penicillin-susceptible (pen-S) and by a pen-R strain with localization of infection to the left lobe and to use the model to evaluate the activity of penicillin and teicoplanin. Two S. pneumoniae strains were used: a pen-S S. pneumoniae type 2 strain and a clinical S. pneumoniae serotype 6B isolate with high resistance to penicillin and it was attempted to establish the model in immunocompetent (pen-S and pen-R strains) and neutropenic rats (pen-R strain).

Materials and methods

Antimicrobial agents

Teicoplanin (Gruppo Lepetit S.p.A., Milan, Italy), was used for both in-vitro and in-vivo studies. A pharmaceutical preparation of procaine penicillin G (Streuli & Co. A G, Uznach, Switzerland) was used in the experimental treatment.
infections. For in-vitro work and analytical purposes we used procaine penicillin G powder obtained from Sigma Chemical Co. (St Louis, M O, U SA).

Bacterial strains

A virulent variant of the strain S. pneumoniae type 2 ATCC 6302, isolated from a rat that developed a lung infection after intratracheal inoculation of the original strain, was used in the pen-S pneumonia model. A clinical isolate of S. pneumoniae serotype 6B clone was used in the pen-R pneumonia model. This strain was kindly provided by Dr K. G. Kristinsson (National University Hospital, Reykjavik, Iceland) and has been described previously. The isolates were stored in small aliquots at −80°C in brain heart infusion broth (Difco Laboratories, Detroit, M I, U SA) supplemented with 5% (v/v) filtered heat-inactivated horse serum (Sclavo, Siena, Italy) and 20% (v/v) glycerol (Farmitalia C. Erba, Milan, Italy). Confirmation of identity as S. pneumoniae was made by rapid ID 32 strep (Bio Mérieux SA, Marcy-l’Etoile, France), colonial morphology, observation of α-haemolysis when grown on blood agar and sensitivity to optochin discs (BBL Microbiology Systems, Cockeysville, M D, U SA).

Antibiotic susceptibility studies

MICs of procaine penicillin G and teicoplanin were determined by the broth microdilution method. Inocula were prepared from logarithmic-phase cultures grown in Mueller–Hinton broth (Difco) supplemented with cations and 5% (v/v) fetal calf serum at 35°C in a 5% CO₂ atmosphere to yield a bacterial concentration of approximately 5 × 10⁸ cfu/mL. A nontoxins were serially diluted in two-fold steps with each tube containing 1 mL of broth. Pneumococci were incubated for 24 h at 35°C in a 5% CO₂ atmosphere. The MIC was defined as the lowest concentration of antibiotic that prevented visible growth. The MBC was determined by plating duplicate 0.01 mL samples from tubes with no visible growth on to Difco Columbia agar plus 5% (v/v) sheep blood after 48 h of incubation at 35°C in a 5% CO₂ atmosphere. The MBC was defined as the lowest concentration of antibiotic that killed ≥99.9% of the original inoculum.

Preparation of inocula for infections

An aliquot of the frozen culture of each strain was thawed and inoculated into brain heart infusion broth containing 5% (v/v) filtered heat-inactivated horse serum for the pen-R model in normal rats or supplemented with 0.2% agar for the pen-S model in normal rats and pen-R model in neutropenic rats. Cultures were incubated at 35°C in a 5% CO₂ atmosphere until the optical density (at 625 nm) reached approximately 0.3, corresponding to a bacterial titre of approximately 1 × 10⁸ cfu/mL. For preparation of pen-R infection in normal rats, the pen-R logarithmic-phase broth culture was centrifuged at 4300g for 10 min and resuspended in fresh melted brain heart infusion 0.5% agar to adjust the final cell concentration to approximately 1 × 10⁸ cfu/mL. Bacterial titres were confirmed by plating serial ten-fold dilutions on to Difco Columbia agar plus 5% sheep blood just before infection of the animals.

Induction of neutropenia in rats

Rats were treated intraperitoneally with 80 mg of cyclophosphamide (Asta Medica A G, Frankfurt, Germany) per kg of body weight on days −4 and −1 (before infection). The animals were housed throughout the experiment in a cabinet ventilated with air filtered by a HEPA filter. A group of five animals was reserved for monitoring neutropenia. Blood was collected from the tail vein just before the first cyclophosphamide treatment and 24 h after the last treatment. Total leucocyte counts were determined visually with a Bürker counting chamber. Differential count was determined by microscopic examination after staining with May–Grünwald–Giemsa stain (E. Merck, Darmstadt, Germany). The leucocyte counts fell from a pretreatment mean of 12,100/μL (c.15% granulocytes) of blood to a mean of 520/μL (c.8% granulocytes) of blood at the time that the other groups of animals were infected (24 h after the second cyclophosphamide treatment). Previous studies indicated that neutropenia persists for at least 6 days after the end of cyclophosphamide treatment (data not shown).

Experimental pneumonia

Pneumonia was induced in female CD rats (Charles River Breeding Laboratories, Calco, Italy), weighing approximately 100–150 g at the time of infection. The animals were housed in plastic cages, fed with standard diet 4R F21 (Charles River Laboratories, Settimino Milanese, Italy) and were allowed free access to water. Under aseptic conditions, a small incision was made in the skin overlying the trachea. The trachea was exposed by blunt dissection and then punctured with a pair of fine operating scissors. A sterile blunt-tipped curved needle (18-gauge), to which was attached a 1 mL syringe fixed to a microsyringe repeating dispenser (Hamilton Bonaduz A G, Bonaduz, Switzerland), was inserted into the left main stem bronchus through the tracheal puncture. The pneumococcal suspension (0.04 mL) was instilled into the lower tract of the left lung. The inocula were 2–4 × 10⁶ cfu per rat for pen-S S. pneumoniae strain, 2–5 × 10⁷ cfu per rat for pen-R S. pneumoniae.
strains in immunocompetent rats and $3 \times 10^6$ cfu per rat in neutropenic rats. The external wound was closed with sterile metal clips. After infection, rats were maintained with their heads elevated for at least 20 min to facilitate distal alveolar migration of the bacteria by gravity.

### Assessment of the model

**Determination of bacterial loads in lung tissue of rats inoculated with either pen-S or pen-R S. pneumoniae** was performed only on immunocompetent animals. Groups of five or six infected, untreated rats were killed at various intervals up to day 7 after infection. Parameters for monitoring the infection were total body weight, macroscopic examination of lung lesions, and quantification of the number of viable bacteria in lungs and blood.

### Antimicrobial therapy

In each experiment, a group of animals was killed 12 h after bacterial inoculation, just before the first antibiotic treatment in order to provide pre-treatment bacterial counts. Teicoplanin was given as a single iv dose at 5 or 10 mg/kg in the experiments with normal rats and at 10 or 20 mg/kg in the experiment with neutropenic rats. Procaine penicillin G was administered intramuscularly at 12-hourly intervals for 3 days at the following doses: 10,000 IU/kg in the pen-S model; 10,000 or 80,000 IU/kg in the pen-R model in immunocompetent rats and 100,000 IU/kg in the neutropenic rats.

### Pharmacokinetic studies

In each experiment, groups of 2–4 infected rats were used to determine the plasma kinetics of administered compounds. Plasma samples were taken into heparinized tubes by puncture of the retro-orbital sinus of anaesthetized rats (Fluothane, Zeneca Ltd, Macclesfield, U.K.) up to 72 h following iv administration of teicoplanin (5 and 10 mg/kg) and up to 12 h after the fifth im administration of procaine penicillin G at 10,000 and 80,000 IU/kg. Concentrations were determined by agar diffusion method, using Micrococcus luteus ATCC 9341 for procaine penicillin G and Bacillus subtilis ATCC 6633 for teicoplanin. The assays were done with the 2 + 2 design described in Appendix XIV A of the British Pharmacopoeia. Limit of quantification were 0.05 mg/L for procaine penicillin G and 0.2 mg/L for teicoplanin and the statistical accuracy was determined to be 10% at the 95% confidence level.

Twelve hours after the last procaine penicillin G treatment or 72 h after the single dose of teicoplanin (84 h after infection), all surviving rats were killed by ip injection of an overdose of Pentothal Sodium (A bbott S.p.A., Latina, Italy). A assessment of infection and therapy

After rats had been killed, the chest cavity was opened and blood for bacterial culture was collected by cardiac puncture into a sterile microtube containing a few microlitres of saline plus 1% (w/v) sodium polyanethole-sulphonate (Sigma) as anticoagulant. AFTER macroscopic examination, the lungs were removed aseptically, dissected free of the trachea and bronchi and homogenized together in 5 mL of 0.9% (v/v) NaCl-0.1% (w/v) Difco peptone (Difco). The homogenates were centrifuged and the deposits suspended in the same volume of Oxoid No. 2 Nutrient broth (Unipath Ltd, Basingstoke, U.K.) plus 20% (v/v) glycerol. To reduce antibiotic carry-over effects, duplicate aliquots (0.025 mL) of suitable dilutions (at least ten-fold) of blood or lung homogenates in PBS were plated by inclusion in 2.5 mL of Difco Columbia broth containing 0.7% agar, on Difco Columbia agar plus 5% sheep blood. Colonies were counted after incubation at 35°C for 48–72 h. Bacterial titres were expressed as $\log_{10}$ cfu/mL of blood or $\log_{10}$ cfu in the two lungs. Blood and lung samples were considered sterile when no growth occurred from the two undiluted 0.025 mL samples; in this case, for calculation of the mean number of cfu/mL of blood or per organ, the samples were considered to contain 1 cfu per 0.05 mL, which corresponded to $\leq 1.3 \log_{10}$ cfu/mL of blood or $\leq 2 \log_{10}$ cfu/organ.

### Histopathological examinations

For evaluation of the histopathological changes in lung tissue resulting from intratracheal inoculation with pen-S or pen-R S. pneumoniae in immunocompetent rats, groups of vehicle-inoculated rats and rats inoculated with both pen-S and pen-R strain were killed at various time points after infection. Lungs, trachea and bronchi were removed together, fixed by perfusion with 10% buffered neutral formalin, and stored in the same solution. The organs were fixed in Davidson’s fluid before being embedded in paraffin blocks, sectioned and stained with haematoxylin and eosin. The histopathological examinations were performed in the Institute of Biomedical Research ‘Antoine Marxer’, RBM S.p.A., Ivrea, Italy.

### Statistical analysis

Statistical differences in plasma concentrations/dose between the models were tested by ANOVA. Bacterial titres were examined by ANOVA for multiple comparisons by using the SAS GLM procedure. By this analysis, $P$ was corrected for multiple comparisons ($P’$) by using the formula $P’ = 1 - (1 - P)^n$ where $n$ is the number of preplanned comparisons. Differences in the numbers of sterile samples between controls and treated groups were analysed by Fisher’s exact probability test.
Results

Antibiotic susceptibility studies

A gainst the pen-S S. pneumoniae strain, teicoplanin and penicillin had similar in-vitro activities (MIC/MBC: 0.03/0.06 mg/L and 0.06/0.06 mg/L, respectively). Against the pen-R S. pneumoniae strain, teicoplanin had MIC and MBC values at least 30-fold lower than those of procaine penicillin G (0.06/0.12 mg/L and 2/4 mg/L, respectively) (Table I).

Gross pathology

After intratracheal injection with either pen-S or pen-R S. pneumoniae strains in normal rats, a chronic non-fatal pneumonia developed within 12 h. At that time the lungs were macroscopically normal in appearance, except for an area that was red in colour and was confined to the lower portion of the left lobe, which was the intended site of inoculation. By 90 h the inflammation covered almost the entire left lobe, which had a hard consistency. By 138 h, several rats showed spread of the inflammation to the right lobes. Infected rats had significant symptoms of illness: shortness of breath and rapid breathing, reduced activity and moderate loss of body weight within 2 days of infection.

Bacteriology

Figure 1 shows the time-course of bacterial infection, by viable counts in lungs, in immunocompetent rats infected with pen-S and pen-R S. pneumoniae strains following intratracheal inoculation of either organism. Pneumococci were recovered from the lungs of all infected rats throughout the course of the infection. A fter inoculation, the average bacterial lung load increased to approximately \(10^7-10^8\) cfu per pair of lungs on days 1-3 and persisted at these levels up to day 7 after infection (Figure 1). On most days less than half of the rats had positive blood cultures and cfu/mL blood were generally low. High-level bacteraemia (almost \(10^7\) cfu/mL of blood) was occasionally recorded in several rats, in most cases accompanied by pleurisy. Although survival rates, determined in a separate group of eight or nine rats, were about 70% for rats infected with both strains, the survival time was different; rats challenged with the pen-S strain died in the later stages of infection, whereas for rats infected with the pen-R strain the critical period for survival was between 12 and 36 h after infection.

Histopathological examinations

Microscopic examination of lung tissues from rats infected intratracheally with either pen-S or pen-R S. pneumoniae strains showed similar infection patterns. Inflammatory changes of the left lobe that evolved from an acute to a subacute form of lobar pneumonia were observed in both groups of infected animals and were accompanied by massive and intense infiltration of polymorphonuclear leucocytes in alveoli and by oedema. Bacterial colonies were observed in alveoli of the left and right lobes and in the pleura of these animals, indicating spread of the infection within the lungs and pleural cavity from the point of inoculum. Intratracheal administration of brain heart broth plus 0.5% agar suspensions (vehicle) induced a slight alveolar histiocytosis in rats killed on day 1 of inoculation only, whereas no inflammatory reaction was observed in rats killed subsequently.

Antibiotic efficacy

Activity in immunocompetent rats. Table I shows the results of treatments of two pneumococcal infections caused either by pen-S or pen-R strains in immunocompetent rats. Six im injections of procaine penicillin G, 10,000 IU/kg body weight, produced a significant reduction in the number of rats infected with the pen-S strain (P < 0.001 as compared with untreated control), but not in those infected with the pen-R strain. A n eight-fold higher dosage twice-daily of procaine penicillin G produced a significant reduction in mean lung bacterial loads of rats infected with pen-R strain as compared with the untreated control group (P < 0.01) and with the group treated with the lower procaine penicillin G regimen (P < 0.05).

In both infections, a single iv dose of teicoplanin 5 mg/kg or 10 mg/kg body weight was highly efficacious (P < 0.001) in reducing the lung bacterial loads as compared with untreated controls. Experiments with the pen-S strain demonstrated that the group treated with the higher dosage of teicoplanin had a mean lung bacterial load significantly lower than that of the group treated with the lower dose (P < 0.05). Similarly the number of animals with a significant number of lung samples with bacterial counts below the level of detection (P < 0.001) was increased compared with untreated controls. Bacterial counts of rats treated with both teicoplanin regimens were significantly lower than those of rats treated with procaine penicillin G 6 x 10,000 IU/kg body weight (P < 0.001).

Positive blood cultures were seen in a few pen-S-infected untreated rats: low numbers of bacteria were recovered from blood of these rats. A mong rats infected with the pen-R strain, four of seven surviving untreated rats at the end of the experiment had S. pneumoniae in the blood. Treatment with both teicoplanin regimens reduced blood bacterial counts to undetectable levels in most rats infected with both of the strains.

Neutropenic pen-R model. The therapeutic efficacies of teicoplanin and procaine penicillin G in the pen-R
Table I. Activity of teicoplanin and procaine penicillin G in 3-day therapy of pen-S and pen-R *S. pneumoniae* pneumonia in the immunocompetent rat

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>Dose</th>
<th>MIC/MBC(^a) (mg/L)</th>
<th>Pen-S <em>S. pneumoniae</em></th>
<th>Pen-R <em>S. pneumoniae</em></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>no. of survivors/total</td>
<td>mean ± S.D. (\log_{10}) cfu/ (\log_{10}) cfu/mL</td>
<td>no. of survivors/total</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>in lungs (^b)</td>
<td></td>
</tr>
<tr>
<td>Pretreatment(^c)</td>
<td>8/8</td>
<td>8.0 ± 0.4</td>
<td>2.3 ± 2.2</td>
<td>9/9</td>
</tr>
<tr>
<td>None</td>
<td>8/8</td>
<td>8.1 ± 0.3</td>
<td>1.6 ± 0.7</td>
<td>7/9</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>10 mg/kg</td>
<td>0.03/0.06</td>
<td>2.1 ± 0.2(^d)(^e) (2(^d))</td>
<td>0.06/0.12</td>
</tr>
<tr>
<td>Teicoplanin</td>
<td>5 mg/kg</td>
<td></td>
<td>2.8 ± 0.6(^e)</td>
<td>1.3</td>
</tr>
<tr>
<td>Procaine penicillin G</td>
<td>10,000 IU/kg</td>
<td>0.06/0.06</td>
<td>4.5 ± 0.5(^d)</td>
<td>1.3</td>
</tr>
<tr>
<td>Procaine penicillin G</td>
<td>80,000 IU/kg</td>
<td>ND/ND</td>
<td>ND</td>
<td>ND</td>
</tr>
</tbody>
</table>

\(^a\) Activities determined in Mueller–Hinton broth by macrodilution method with an inoculum of \(5 \times 10^5\) cfu/mL.

\(^b\) No. of positive cultures in parentheses.

\(^c\) Determined in a separate group of infected animals just before the first treatment.

\(^d\) \(P < 0.001\) versus untreated controls.

\(^e\) \(P < 0.001\) versus procaine penicillin G 10,000 IU/kg.

\(^f\) \(P < 0.05\) versus teicoplanin 5 mg/kg.

\(^g\) \(P < 0.05\) versus procaine penicillin G 80,000 IU/kg.

\(^h\) \(P < 0.05\) versus procaine penicillin G 10,000 IU/kg.

\(^i\) \(P < 0.05\) versus untreated controls.

ND, Not determined.
The course of infection was more severe than in normal rats as demonstrated by the higher mortality rate in the untreated control group. For example, only one of six rats survived the infection and in this animal high numbers of *S. pneumoniae* were cultured from both lungs and blood (Table II).

Pharmacokinetics. Mean plasma concentrations of teicoplanin in pen-S and pen-R-infected animals following a single 5 mg/kg or 10 mg/kg iv dose are shown in Figure 2. Following administration, concentrations were high and prolonged, being detectable up to 30 h after the lower dose and up to 48 h after the higher one. The concentration–time profiles declined with an apparent triexponential behaviour, as previously reported.16 As indicated by the extrapolated part of the curve that best interpolates the experimental data, teicoplanin plasma concentrations following both doses were in excess of the MIC for both study organisms throughout the experiment (Figure 2).

Mean plasma concentrations of penicillin G in pen-S- and pen-R-infected animals obtained after the fifth iv administration of a 10,000 or 80,000 iu/kg dose are shown in Figure 3. Peak plasma levels were achieved within 15 min after administration of both doses. A biexponential model best described the pharmacokinetic behaviour of this compound. Elimination was rapid, penicillin being detectable in plasma up to 2 h after the lower dose and up to 8 h after the higher one. As shown by the extrapolated curve, the 10,000 IU/kg dose given 12 hourly resulted in penicillin G plasma concentrations that remained above the MIC for the sensitive strain for 2.75 h and above that...
for the resistant strain only for about 20 min (Figure 3). For the 80,000 IU/kg dose plasma concentrations exceeded the MIC for the pen-S strain for 11 h and for the pen-R strain for 2.5 h.

**Discussion**

**The infection model**

Our first attempts to produce a lobar pneumonia, with a pen-R *S. pneumoniae* strain, were made by using cyclophosphamide-treated animals with reduced immunological defences, in order to induce susceptibility to the infection. Several pen-R clinical isolates, belonging to serotypes 6, 14, 19 and 23, were tested in these experimental conditions. The pen-R *S. pneumoniae* strain that emerged from the screening experiments, and used in the studies reported here, was particularly virulent, causing 100% mortality of control animals within 44 h after infection and often failing to produce a well-developed pneumonia. Smaller challenge inocula caused similar or somewhat less mortality, but with most deaths occurring in the later stages of the infection (84 h after infection) and produced a lobar pneumonia. The high virulence of the strain led us to test it in immunocompetent animals to see if it was able to provoke a lobar pneumonia. The rats showed a course of infection, including microbiological aspects, gross pathological changes and mortality rates, similar to those seen in the pen-S model, although the number of pneumococci recovered from lungs of pen-R-infected rats was quite variable.

The use of very young rats, which are thought to be more susceptible to infection and a higher per cent of melted agar enmeshed with bacterial suspension as growth-promoting agent, were crucial in establishing a reproducible non-fatal experimental model with a consolidated lobar pneumonia in immunocompetent rats. In contrast, during the period of severe neutropenia, rats infected with the same strain exhibited a course of infection more severe than in normal rats, as determined by the mortality and the presence of large numbers of pneumococci in the blood of the surviving untreated rat.

**Treatment of experimental infection**

The efficacy of procaine penicillin G and teicoplanin in pneumonia experiments reflected the intrinsic in-vitro activity against the microorganisms tested and the time for which plasma concentrations exceeded the MIC for the strains. In immunocompetent animals treated with teicoplanin, a single iv dose of 5 mg/kg given 12 h after infection was able to reduce significantly the bacterial loads of the lungs of rats infected with about $10^6$ cfu of pen-S *S. pneumoniae* or with about $10^6$ cfu of pen-R *S. pneumoniae* as compared with untreated controls. In both models, the plasma concentrations generated by the 5 mg/kg and the 10 mg/kg dose were greater than the MIC for the strains throughout the study period. However, a significantly greater reduction in mean lung bacterial load, with the higher compared with the lower dose, was observed only for the susceptible strain. The small number of animals used in the experiments, other differences between the infecting strains apart from their different penicillin susceptibilities, or other unidentified factors might have been responsible. The efficacy of teicoplanin appears to be dose-dependent even at concentrations in plasma greatly in excess of the MIC, as previously described.

In cyclophosphamide-treated animals infected with the pen-R strain, a single dose of teicoplanin 10 mg/kg did
not significantly reduce the lung bacterial load compared with untreated controls, whereas the 20 mg/kg regimen was more effective. A possible explanation may be the late start of treatment (12 h), by which time the infective process was severe and difficult to eradicate. However, such high doses of teicoplanin are not usually recommended for treatment in man.

Higher doses and/or more frequent dosing of procaine penicillin G might have been more efficacious. Schmidt & Walley reported that penicillin G was considerably more effective in curing rats with pneumococcal pneumonia when administered at 8 h intervals than when given in either more frequent or more widely spaced doses. These investigators used the sodium salt of penicillin G, a formulation that permits high and rapid peaks of the drug in the blood after im injection, but also equally rapid excretion. Procaine penicillin G used in our studies is a long-acting formulation of penicillin which in humans achieves moderate serum levels that can be maintained for 12–24 h depending on the dose. Therefore, we used the dosing interval of procaine penicillin G 12 hourly as conventionally is employed in humans.

The models of lobar pneumonia caused either by pen-S or pen-R S. pneumoniae strains described here resemble human disease with respect to clinical, microbiological and histopathological changes. Infected animals yielded remarkably similar and reproducible numbers of bacteria. Hence, the two immunocompetent models should be useful in the preliminary assessment of the potential therapeutic role of antibiotics in terms of recovery of pneumococci from lungs, whereas additional information on survival rates should be drawn by the immunocompromised pen-R model.

Extrapolation of these experimental data to the clinical situation must be performed with caution. However, the demonstration that teicoplanin is active in vivo, albeit at high doses, in these models of lobar pneumonia merits further study for the treatment of penicillin-resistant pneumococcal infections.

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References


Teicoplanin in experimental pneumonia


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