Endothelial Apoptosis

To the Editor:

We read with interest the excellent review by Stefanec (March 2000), which summarized the knowledge about endothelial apoptosis. Table 2 of this article represented the pro- and antiapoptotic stimuli for endothelial cells. Herein, we would like to add activating sis. Table 2 of his article represented the pro- and antiapoptotic (PPAR)-

Table. Activation of peroxisome proliferator-activated receptor (PPAR)-γ is also recognized to induce endothelial apoptosis.5 PPARs are members of the nuclear hormone receptors superfamily of ligand-activated transcriptional factors that include receptors for steroids, thyroid hormone, vitamin D, and retinoic acid.3 Among PPARs (-α, -γ, and -δ), PPAR-γ is expressed in adipose tissue and the immune system such as the splenocytes, monocytes, and bone marrow precursors, and it plays important roles in adipocyte differentiation, anti-inflammatory process, and growth arrest of tumor cells.5 In addition, recent data have shown that natural prostaglandin 15-deoxy-12,14-prostaglandin J2 and the synthetic antidiabetic thiazolidinediones, which are PPAR-γ ligands, induce apoptosis in macrophages, fibroblasts, cancer cells, and endothelial cells.2,5,6 Hence, PPAR-γ may become a novel therapeutic target as a proapoptotic stimulus.

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Fatal Pneumococcal Pneumonia Attributed to Macrolide Resistance and Azithromycin Monotherapy

To the Editor:

We report a fatal case of bacteremic pneumococcal community-acquired pneumonia (CAP) treated initially with azithromycin, where the failure of antibiotic therapy was at least partially attributable to macrolide resistance.

A 49-year-old white woman presented to another hospital with a 3-day history of fever and cough productive of thick yellow sputum. Hypothyroidism, treated with thyroid hormone, and gastric bypass surgery for obesity were the only significant past medical conditions. Her body mass index at the time of admission was 23.8.

On examination, her temperature was 38.0°C, heart rate was 113 beats/min, respiratory rate was 20 breaths/min, and BP was 90/50 mm Hg. Oxygen saturation was 92% by oximetry on room air. Coarse crackles were present at both lung bases on chest auscultation. There were no other abnormal findings. Laboratory studies showed a total WBC count of 6.2 × 10^6 cells/L. Except for mild hypokalemia (3.3 mmol/L), electrolytes, renal, and hepatic function tests were all normal. A chest radiograph showed consolidation in both lower lobes, with more dense consolidation on the right than on the left.

She was admitted, and IV azithromycin, 500 mg/d, was commenced. Her pneumonia severity index grade 1 on admission was 2, and her APACHE (acute physiology and chronic health evaluation) II score, based on the worst physiologic variables during the first 24 h, was 9, giving a predicted mortality of 10%.

Over the next 48 h, she remained stable but did not show any signs of clinical improvement. Her temperature remained elevated, peaking at >39.0°C each day, and she had persistent tachycardia at 110 to 130 beats/min, but her systolic BP did not drop to <90 mm Hg.

Approximately 72 h after admission, she became hypotensive and required intubation. When seen by a pulmonary/critical-care physician, she was noted to be normothermic, but had a heart rate of 140 beats/min and a BP of 70/30 mm Hg despite a dopamine infusion of 10 g/kg/min. Her WBC count had also increased to 30.4 × 10^9 cells/L. There was no clinical, biochemical, or ECG evidence of myocardial ischemia. Fluid resuscitation and an increase in isotropic treatment of septic shock, including a norepinephrine infusion, were commenced. Levofloxacin, 500 mg, and vancomycin, 1,000 mg, were also added to the antibiotic regimen.

Despite all measures, including full intensive care support, she died <72 h after the onset of septic shock. Blood and sputum cultures subsequently grew Streptococcus pneumoniae sensitive to penicillin, cephalosporins, and quinolones but resistant to erythromycin, with a minimal inhibitory concentration (MIC) of 16 g/mL (determined by E-strip diffusion and subsequently confirmed by repeat culture).

Macrolide monotherapy is not recommended for hospitalized patients by either the American Thoracic Society or Infectious Disease Society of America CAP guidelines. However, it has recently been suggested that azithromycin monotherapy may be appropriate in this setting.

In our experience, the development of septic shock several days after presentation with pneumonia is unusual. Given the absence of other significant medical problems, we believe failure of antibiotic therapy contributed to the ultimately fatal outcome in this case. It has been suggested that clinical resistance to azithromycin, because of its superior pharmacokinetics, should not develop at the MIC of erythromycin (<32 g/mL). There are, however, very little data from clinical studies to support this assumption. Although vancomycin and levofloxacin were added to the antibiotic regimen, this was after the development of severe septic shock. The patient also died within 48 h of the change in therapy, giving these antibiotics little chance of modifying the outcome.

In conclusion, we have reported a case of CAP that we believe had a fatal outcome due to failure of azithromycin monotherapy in the setting of relatively low-level macrolide resistance. Physicians in areas with a high prevalence of macrolide-resistant pneumococci