Effects of different anaesthetics on cytokine levels in children with community-acquired pneumonia undergoing flexible fibreoptic bronchoscopy

Lin Chen¹,², Jing Cheng² and Yan-Lin Wang¹

Abstract

Objective: To determine the effects of propofol and sevoflurane on cytokine levels in children with community-acquired pneumonia undergoing flexible fibreoptic bronchoscopy (FFB).

Method: Children with community-acquired pneumonia were randomly assigned to receive 3–5 mg/kg propofol i.v. or 8% inhaled sevoflurane. Haemodynamic variables, stress hormone responses and serum cytokines were compared between the two groups.

Results: Out of 50 children aged 2–12 years (propofol, n = 25; sevoflurane, n = 25), there were no significant between-group differences in haemodynamic variables and stress hormones. Interleukin (IL)-6 and IL-10 decreased significantly following FFB in both groups. IL-6 levels were significantly lower in the sevoflurane group than propofol group at 4 h and 1 d following FFB (61.3 ± 11.9 versus 82.6 ± 19.7 pg/ml; 52.8 ± 9.7 versus 75.4 ± 13.6 pg/ml, respectively). IL-10 levels in the sevoflurane group were significantly lower than in the propofol group at 1 d following FFB.

Conclusions: In children with community-acquired pneumonia, use of sevoflurane was associated with lower circulating IL-6 and IL-10 levels compared with propofol, following FFB. Pneumonia severity is reflected by higher blood cytokine levels, thus, sevoflurane may be more beneficial to recovery from community-acquired pneumonia than propofol, however further studies are required to test this hypothesis.

Keywords
Bronchoscopy, cytokines, physiological, propofol, sevoflurane, stress

Date received: 29 July 2015; accepted: 27 January 2016

¹Department of Anaesthesiology, Zhongnan Hospital, Wuhan University, Wuhan, China
²Department of Anaesthesiology, Hubei Maternal and Child Health Hospital, Wuhan, China

Corresponding author:
Yan-Lin Wang, Department of Anaesthesiology, Zhongnan Hospital, Wuhan University, 169 Donghu Road, Wuhan, 430071, China.
Email: znyywyl@hotmail.com

Creative Commons CC-BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 3.0 License (http://www.creativecommons.org/licenses/by-nc/3.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access page (https://us.sagepub.com/en-us/nam/open-access-at-sage).
Introduction

Community-acquired pneumonia continues to be a common and serious illness in children. The host’s inflammatory response to microorganisms involved in community-acquired pneumonia is associated with the release of proinflammatory and anti-inflammatory cytokines, however excessive cytokine production can cause deleterious effects. The severity of pneumonia is both reflected and predicted by higher levels of cytokines in the blood.

Flexible fibreoptic bronchoscopy (FFB) is a technique that allows direct visualization of the tracheobronchial tree for diagnostic and therapeutic purposes in community-acquired pneumonia. During FFB, there are two factors that can influence serum cytokine levels. First, as an invasive procedure, FFB can irritate and damage the airway mucosa, activate the hypothalamic pituitary adrenal axis, and then induce the stress response and changes in immune function. Secondly, anaesthetics used during FFB may have immunomodulatory properties, and can inhibit the release of cytokines. Although these effects may be inconsequential in children with a normal functioning immune system, suppression of the immune response may have relevance in children with a pre-existing immune imbalance, for example in cases of community-acquired pneumonia.

Sevoflurane and propofol are widely used in the induction and maintenance of anaesthesia during FFB in children. To the best of the authors’ knowledge, there has been little work focusing on the relationship between these two anaesthetics and cytokine release in children with community-acquired pneumonia undergoing FFB.

In the present study, serum cytokines and stress hormones were compared in children with community-acquired pneumonia undergoing FFB, to investigate the immunomodulatory effects of sevoflurane and propofol.

Patients and methods

Study population

This randomized parallel-group trial was conducted at Hubei Maternal and Child Health Hospital, Wuhan, China between March 2015 and May 2015. Inclusion criteria comprised male and female children aged 2–12 years with a clinical diagnosis of community-acquired pneumonia undergoing FFB; and children classified with American Society of Anaesthesiologists physical status (ASA) II or III. A diagnosis of community-acquired pneumonia was defined as radiographic evidence of pulmonary infiltrate consistent with acute infection requiring antibiotic therapy, and the presence of two or more indications of pneumonia: fever, shortness of breath, cough, chest pain, abnormal white blood cell count or physical signs of pneumonia on examination (e.g., rales on auscultation, dullness to percussion, or egophony). Children with a history of immunosuppression, neutropenia, cardiovascular, endocrinological, hepatic or renal disorders, allergy to opioids, or recent use (within 3 months prior to study entry) of analgesics or psychoactive drugs were excluded from the study. Children who had experienced FFB within 3 months prior to study entry were also excluded.

The study protocol was approved by Hubei Maternal and Child Health Hospital Ethics Committee (Protocol number: 2015008, Date: March 2nd, 2015) and registered at www.chictr.org (ChiCTR-TRC-15006031). This study was conducted according to the Declaration of Helsinki. Written informed consent was obtained
from the legal proxies of all participants before the trial commenced.

**Study design**

All FFB procedures were performed during morning hours. Children were randomized at study entry, using a computer-generated list, into a propofol group or sevoflurane group. Coded, sealed envelopes were used for allocation concealment. The propofol group received 3–5 mg/kg propofol i.v. infusion, while the sevoflurane group received oxygen at a flow of 6 l/min and 8% sevoflurane by inhalation using a Dräger Fabuis GS Anaesthesia Machine (Dräger Medical AG & Co. KG, Lubeck, Germany); both groups received 1 mg/kg remifentanil i.v. injected for 60 s followed by 0.4 μg/kg/min remifentanil by i.v. infusion. Doses of propofol and sevoflurane were adjusted to keep the bispectral index between 40 and 50. The bronchoscope (Olympus Corporation, Tokyo, Japan) was introduced through a bronchoscopy adapter (Covidien LLC, MA, USA) and a laryngeal mask airway (WEILI Corporation, Guangzhou, China). Upon direct visualization of the vocal cords, 1% lidocaine (maximum 7 mg/kg) was injected for topical anaesthesia. Bronchoalveolar lavage was performed using 0.9% NaCl (maximum 5 mg/kg). All drugs were discontinued upon completion of the FFB procedure, and the laryngeal mask airway was removed when the children were fully awake.

Phenylephrine (0.05 mg/kg, i.v.) was administered when mean arterial pressure was ≥30% reduction from baseline, and could not be controlled within 5 min by increasing the level of fluid infusion. Atropine (0.01 mg/kg, i.v.) was administered when heart rate was <80 beats per min.

**Data collection**

Heart rate and mean arterial pressure were monitored and recorded at baseline (T₀), on completion of FFB (T₁) and 4 h following FFB (T₂). Duration of the FFB procedure was also recorded.

Venous blood samples (3 ml) were taken at six time points: at baseline (T₀); on completion of FFB (T₁); 4 h following FFB (T₂); at 1 day following FFB (T₃); at 4 days following FFB (T₄); and at 7 days following FFB (T₅). The samples were drawn into tubes without anticoagulants, and cooled overnight at 4°C before centrifugation at 1000 g for 15 min at 4°C. Serum samples were then collected and stored at −20°C prior to use. Serum levels of stress hormones (noradrenaline, adrenaline and cortisol, measured at T₀, T₁ and T₂) and the cytokines tumor necrosis factor (TNF)-α, interleukin (IL)-6 and IL-10 were determined by enzyme-linked immunosorbent assay using commercial kits (Human Noradrenaline ELISA, Human Adrenaline ELISA, Human Cortisol ELISA, Human Cytokine TNF-α ELISA, Human Cytokine IL-6 ELISA and Human Cytokine IL-10 ELISA; Wuhan Xinqidi Biological Technology Co., Ltd, Wuhan, China) according to the manufacturer’s instructions. A WHYM201 Elisa Microplate Reader (Poweam Medical Systems Co., Ltd, Jiangsu, China) was used to analyse the ELISA reactions.

**Statistical analyses**

The number of patients required for each study group was estimated according to the between-group differences in serum IL-6 levels observed in the authors’ previous pilot study (data not shown). It was estimated that to have 80% power of detecting a 30% difference with a type-I error of 5%
using Chinese High Intellectualized Statistical Software (CHISS 2010; Yuanyitang Science & Technology, Beijing, China), a minimum of 22 children were required in each group. A 10% drop-out rate was anticipated, thus, a minimal sample size of 25 was recruited for each group. Data are presented as mean ± SD or n prevalence. Student’s $t$-test was used to compare between-group age, weight, and duration of FFB. $\chi^2$-test was used to analyse categorical data. Two-way repeated measures analysis of variance followed by multiple comparisons (least significant difference testing) was used to evaluate the effects of time, group, and interaction. Statistical analyses were performed with SPSS® software, version 13.0 (SPSS Inc., Chicago, IL, USA) for Windows®. A $P$ value < 0.05 was considered statistically significant.

Results

Out of 56 eligible children initially enrolled, 50 were finally included in the study (25 received propofol and 25 received sevoflurane); six children were excluded because they refused to participate (Figure 1). There were no statistically significant between-group differences in demographic details or duration of FFB (Table 1). There were also no statistically significant between-group differences in type of infection (bacterial or non-bacterial pneumonia) or numbers who received steroid therapy (Table 2).

Heart rate and mean arterial pressure decreased in both groups at the end of FFB ($P = 0.003, P = 0.004$) compared with baseline, and there were no statistically significant between-group differences in these parameters at T0, T1 and T2 (Table 3). Stress hormones (noradrenaline, adrenaline and cortisol) decreased at the end of FFB (T1) and 4h following FFB (T2) versus baseline ($P < 0.01$), and there were no statistically significant between-group differences at T0, T1 and T2 (Table 3).

Circulating serum IL-6 and IL-10 levels decreased significantly following the FFB procedure in both groups (Table 4). Circulating IL-6 levels were lower in the sevoflurane group than the propofol group at 4 h and 1 day following FFB (61.3 ± 11.9 versus 82.6 ± 19.7 pg/ml, $P = 0.008$; and 52.8 ± 9.7 versus 75.4 ± 13.6 pg/ml, $P = 0.017$, respectively). Circulating IL-10 levels were lower in the sevoflurane group than the propofol group at 1 day following FFB (7.2 ± 2.1 versus 9.5 ± 2.4 pg/ml, respectively, $P = 0.023$). Serum TNF-$\alpha$ was also decreased at 4 days and 7 days following the FFB procedure, and no statistically significant between-group differences were observed in terms of TNF-$\alpha$ at any time point (Table 4).

Discussion

The present study showed that in children with community-acquired pneumonia undergoing FFB, serum IL-6 and IL-10 levels were lower in children who received sevoflurane compared with those who received propofol, suggesting that different anaesthetics might influence the immunological response in these patients. Community-acquired pneumonia is tightly regulated by cytokines produced by the immune system in response to causal microorganisms. These cytokines serve to control infection by leukocyte recruitment and inflammation, however, persistent and toxic inflammation can induce an overly proinflammatory cytokine balance, and lead to poor patient outcomes. Serum IL-6 concentration is a sensitive and specific measurement for assessing response to infection treatment, and might be predictive of death, and rapidity of shock onset. Several studies have shown that IL-6 levels correlate with illness severity in patients with pneumonia. As an anti-inflammatory cytokine, IL-10 is produced primarily by monocytes and Th-2 lymphocytes, and can
inhibit the synthesis of proinflammatory cytokines and suppresses antigen presentation.\textsuperscript{16} High or medium concentrations of IL-6 or IL-10 have been associated with higher mortality in patients with pneumonia, and the highest risk of death when both IL-6 and IL-10 levels were high.\textsuperscript{17}

The present study evaluated changes in cytokine levels associated with two different anaesthetics, propofol and sevoflurane,
in children with community-acquired pneumonia undergoing FFB. The results showed that serum TNF-α, IL-6 and IL-10 levels decreased over time in both groups. One of the main reasons may have been that FFB is beneficial to the identification of infection, and the therapeutic effects of bronchoalveolar lavage may influence treatment outcomes in cases of pneumonia. The present data were in contrast to another study, in which serum proinflammatory cytokines increased following bronchoalveolar lavage in mechanically ventilated patients receiving midazolam sedation throughout bronchoscopy. The main difference between the two studies was selection of agents for sedation/anaesthesia and the experimental subject.

The present study also found that IL-6 was lower in the sevoflurane group at 4 h and 1 day following FFB compared with the propofol group. Two main factors that can induce serum cytokine changes during FFB are stress stimuli and anaesthesia, however, both groups employed the same bronchoscopist and displayed identical serum stress hormone changes, so it may be reasonable to infer that the different anaesthetics influenced the release of cytokines in the present study.

Anaesthetics and sedative agents are known to possess immunomodulatory activities. Propofol pretreatment has been demonstrated to significantly suppress the lipopolysaccharide-induced toll-like receptor 4, monocyte differentiation antigen CD14, and TNF gene expression in an in vitro study. Similar immunomodulatory effects have been shown in vitro for sevoflurane, whereby sevoflurane reduced the release of inflammatory mediators in endotoxin injured alveolar epithelial cells.

### Table 1. Demographic characteristics and duration of flexible fibreoptic bronchoscopy (FFB) in 50 patients with community-acquired pneumonia, aged 2–12 years, who received 1 µg/kg remifentanil and either 3–5 mg/kg propofol or 8% sevoflurane anaesthesia.

| Study group                  | Age, months | Weight, kg | Sex, Female/male | Duration of FFB, min |
|------------------------------|-------------|------------|------------------|----------------------|
| Propofol group (n = 25)      | 34.8 ± 9.6  | 13.5 ± 3.4 | 9/16             | 18.5 ± 6.6           |
| Sevoflurane group (n = 25)   | 35.5 ± 8.1  | 14.1 ± 4.2 | 8/17             | 17.1 ± 5.2           |

Data presented as mean ± SD or n prevalence.

Student’s t-test was used to compare between-group age, weight, and duration of FFB. χ²-test was used to analyse categorical data.

There were no statistically significant between-group differences (P ≥ 0.05).

### Table 2. Type of infection and steroid use in 50 patients with community-acquired pneumonia, aged 2–12 years, who received 1 µg/kg remifentanil and either 3–5 mg/kg propofol or 8% sevoflurane anaesthesia for flexible fibreoptic bronchoscopy.

| Study group       | Characteristic                  |  |
|-------------------|--------------------------------|---|
|                   | Bacterial pneumonia | Non-bacterial pneumonia | Steroid use |
|                   | (n = 25)                                      | (n = 25)                                      | (n = 25)                                      |
| Propofol group    | 11 (44%)                                   | 14 (56%)                                  | 1 (4%)                                   |
| (n = 25)          |                                           |                                           |                                           |
| Sevoflurane group | 12 (48%)                                   | 13 (52%)                                  | 0 (0%)                                  |
| (n = 25)          |                                           |                                           |                                           |

Data presented as n (%) patient prevalence.

There were no statistically significant between-group differences (P ≥ 0.05; χ²-test)
ventilation during lung resection were significantly suppressed by sevoflurane compared with propofol. The mechanism behind this immunomodulation may be reduction of inducible nitric oxide synthase protein levels and nitric oxide synthase activity by decrease in intracellular calcium concentration.

Opioids have also been shown to have immunomodulatory effects. Stimulation of opioid receptors on monocytes leads to a reduction in intracellular cyclic adenosine monophosphate, followed by a reduction in cytokine production. In the present study, both groups received identical opioid regimens, however, children who received sevoflurane showed reduced cytokine levels compared with those who received propofol. This may be because the effect of sevoflurane and propofol on cytokines is due to different mechanisms, and the alveolar epithelial cells may be influenced by direct contact with sevoflurane. In addition, the bronchodilation effect of sevoflurane may make the bronchoalveolar lavage more thorough compared with use of propofol, which may be beneficial to recovery in patients with pneumonia, and thus impact the release of cytokines.

There are some limitations associated with the present study. First, this was a single centre trial and sample sizes are relatively small. Secondly, this study could not be blinded completely due to the odour of sevoflurane, which may have influenced the results relating to duration of bronchoscopy and anaesthesia. Thirdly, the effects of the two agents on long term outcomes, such as antibiotic use, inpatient costs, and patient outcomes, were not studied, and should be

| Table 3. Haemodynamic and hormone values in 50 patients with community-acquired pneumonia, aged 2–12 years, who received 1 μg/kg remifentanil and either 3–5 mg/kg propofol or 8% sevoflurane anaesthesia for flexible fibreoptic bronchoscopy. |
|---------------------------------|----------------|----------------|----------------|
| Parameter                      | Time point     |                |                |
|                                | T<sub>0</sub>  | T<sub>1</sub>  | T<sub>2</sub>  |
| Heart rate, bpm                |                |                |                |
| Propofol group (n = 25)         | 105.2 ± 12.3   | 89.5 ± 8.6<sup>Δ</sup> | 98.3 ± 7.9<sup>†</sup> |
| Sevoflurane group (n = 25)      | 103.6 ± 10.5   | 91.1 ± 9.2<sup>Δ</sup> | 97.9 ± 8.1<sup>†</sup> |
| Mean arterial pressure, mmHg   |                |                |                |
| Propofol group (n = 25)         | 63.2 ± 5.1     | 57.6 ± 4.2<sup>Δ</sup> | 60.3 ± 5.1<sup>†</sup> |
| Sevoflurane group (n = 25)      | 64.1 ± 4.9     | 55.5 ± 4.5<sup>Δ</sup> | 61.4 ± 6.3<sup>†</sup> |
| Cortisol, μg/dl                 |                |                |                |
| Propofol group (n = 25)         | 17.3 ± 2.5     | 8.9 ± 1.8<sup>Δ</sup> | 8.5 ± 2.2<sup>Δ</sup> |
| Sevoflurane group (n = 25)      | 16.8 ± 1.9     | 9.3 ± 1.6<sup>Δ</sup> | 9.1 ± 2.1<sup>Δ</sup> |
| Adrenaline, pg/ml               |                |                |                |
| Propofol group (n = 25)         | 92.5 ± 12.5    | 63.5 ± 10.7<sup>Δ</sup> | 67.3 ± 9.8<sup>Δ</sup> |
| Sevoflurane group (n = 25)      | 88.2 ± 14.7    | 64.7 ± 11.8<sup>Δ</sup> | 69.4 ± 11.5<sup>Δ</sup> |
| Noradrenaline, pg/ml            |                |                |                |
| Propofol group (n = 25)         | 387.5 ± 45.1   | 257.5 ± 34.3<sup>Δ</sup> | 322.7 ± 38.2<sup>Δ</sup> |
| Sevoflurane group (n = 25)      | 391.2 ± 59.8   | 267.8 ± 41.6<sup>Δ</sup> | 315.2 ± 34.8<sup>Δ</sup> |

Data presented as mean ± SD.
ΔP < 0.05 versus baseline; †P < 0.05 versus T<sub>1</sub> (Two-way repeated measures analysis of variance followed by multiple comparisons [least significant difference testing]).
T<sub>0</sub>, baseline; T<sub>1</sub>, end of bronchoscopy; T<sub>2</sub>, 4 h following bronchoscopy; bpm, beats per min.
investigated in a further randomized controlled study. Finally, the aim of the present study was to identify whether there was a difference in patient cytokine levels between use of propofol versus sevoflurane in FFB. The Chinese clinical trial registry [http://www.chictr.org.cn/showprojen.aspx?proj=10501] states that a healthy control group would be recruited to investigate cytokine levels in healthy children versus children with community-acquired pneumonia (propofol and sevoflurane groups). Patients with pneumonia have been shown to display higher levels of cytokines compared with healthy controls,25 therefore, the healthy control group was not recruited.

In conclusion, the present results demonstrated that sevoflurane was associated with decreased circulating IL-6 and IL-10 levels compared with propofol, following FFB in children with community-acquired pneumonia. As the severity of pneumonia is reflected by higher cytokine levels in the blood, it could be inferred that sevoflurane may be more beneficial to the recovery of community-acquired pneumonia compared with propofol, however, further studies are required to test this hypothesis.

Acknowledgements
The authors are grateful to Dr Jiahong Ren for his assistance as the bronchoscopist in this study.

Declaration of conflicting interest
The authors declare that there is no conflict of interest.

| Parameter | Time point | T0 | T1 | T2 | T3 | T4 | T5 |
|-----------|------------|----|----|----|----|----|----|
| TNF-α, pg/ml | Propofol group (n = 25) | 22.3 ± 5.1 | 20.5 ± 4.5 | 19.1 ± 3.9 | 21.8 ± 4.3 | 15.3 ± 3.3 | 13.3 ± 2.9 |
| Sevoflurane group (n = 25) | 20.8 ± 4.8 | 19.9 ± 4.7 | 20.5 ± 4.1 | 20.1 ± 3.5 | 16.1 ± 2.8 | 12.5 ± 2.7 |
| IL-6, pg/ml | Propofol group (n = 25) | 98.5 ± 22.5 | 95.7 ± 22.1 | 82.6 ± 19.7 | 75.4 ± 13.6 | 52.1 ± 8.7 | 33.3 ± 6.2 |
| Sevoflurane group (n = 25) | 96.1 ± 21.7 | 93.9 ± 23.6 | 61.3 ± 11.9 | 52.8 ± 9.7 | 49.6 ± 8.4 | 31.9 ± 7.6 |
| IL-10, pg/ml | Propofol group (n = 25) | 12.1 ± 2.9 | 12.8 ± 2.8 | 10.9 ± 2.5 | 9.5 ± 2.4 | 7.1 ± 1.9 | 6.6 ± 1.7 |
| Sevoflurane group (n = 25) | 10.9 ± 2.7 | 11.5 ± 3.0 | 10.7 ± 2.2 | 7.2 ± 2.1 | 6.9 ± 1.7 | 6.1 ± 1.8 |

Data presented as mean ± SD cytokine level.

*P < 0.05, sevoflurane group versus propofol group; \( ^{\wedge}P < 0.05 \) versus baseline; \( ^{\dagger}P < 0.05 \) versus T2; \( ^{\ddagger}P < 0.05 \) versus T3; \( ^{\ddagger\ddagger}P < 0.05 \) versus T4 (Two-way repeated measures analysis of variance followed by multiple comparisons [least significant difference testing]).

T0, baseline; T1, end of bronchoscopy; T2, 4 h following bronchoscopy; T3, 1 day following bronchoscopy; T4, 4 days following bronchoscopy; T5, 7 days following bronchoscopy; TNF, tumour necrosis factor; IL, interleukin.
References

1. Jain S, Williams DJ, Arnold SR, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. N Engl J Med 2015; 372: 835–845.

2. Menéndez R, Sahuquillo-Arce JM, Reyes S, et al. Cytokine activation patterns and biomarkers are influenced by microorganisms in community-acquired pneumonia. Chest 2012; 141: 1537–1545.

3. Bacci MR, Leme RC, Zing NP, et al. IL-6 and TNF-α serum levels are associated with early death in community-acquired pneumonia patients. Braz J Med Biol Res 2015; 48: 427–432.

4. Fernandez-Serrano S, Dorca J, Coromines M, et al. Molecular inflammatory responses measured in blood of patients with severe community-acquired pneumonia. Clin Diagn Lab Immunol 2003; 10: 813–820.

5. Standiford TJ, Kunkel SL and Strieter RM. Elevated serum levels of tumor necrosis factor-alpha after bronchoscopy and bronchoalveolar lavage. Chest 1991; 99: 1529–1530.

6. Potočnik I, Novak Janković V, Šostarič M, et al. Antiinflammatory effect of sevoflurane in open lung surgery with one-lung ventilation. Croat Med J 2014; 55: 628–637.

7. Yu G, Dymond M, Yuan L, et al. Propofol’s effects on phagocytosis, proliferation, nitrate production, and cytokine secretion in pressure-stimulated microglial cells. Surgery 2011; 150: 887–896.

8. Chen L, Yu L, Fan Y, et al. A comparison between total intravenous anaesthesia using propofol plus remifentanil and volatile induction/maintenance of anaesthesia using sevoflurane in children undergoing flexible fibreoptic bronchoscopy. Anaesth Intensive Care 2013; 41: 742–749.

9. Bradley JS, Byington CL, Shah SS, et al. The management of community-acquired pneumonia in infants and children older than 3 months of age: clinical practice guidelines by the pediatric infectious diseases society and the infectious diseases society of America. Clin Infect Dis 2011; 53: e25–e76.

10. Endeman H, Meijsis SC, Rijikers GT, et al. Systemic cytokine response in patients with community-acquired pneumonia. Eur Respir J 2011; 37: 1431–1438.

11. Fernandez-Botran R, Uriarte SM, Arnold FW, et al. Contrasting inflammatory responses in severe and non-severe community-acquired pneumonia. Inflammation 2014; 37: 1158–1166.

12. Damas P, Canivet JL, de Groote D, et al. Sepsis and serum cytokine concentrations. Crit Care Med 1997; 25: 405–412.

13. Haugen J, Chandyo RK, Brokstad KA, et al. Cytokine concentrations in plasma from children with severe and non-severe community acquired pneumonia. PLoS One 2015; 10: e0138978.

14. Paats MS, Bergen IM, Hanselaar WE, et al. Local and systemic cytokine profiles in nonsevere and severe community-acquired pneumonia. Eur Respir J 2013; 41: 1378–1385.

15. Antunes G, Evans SA, Lordan JL, et al. Systemic cytokine levels in community-acquired pneumonia and their association with disease severity. Eur Respir J 2002; 20: 990–995.

16. Grutz G. New insights into the molecular mechanism of interleukin-10-mediated immunosuppression. J Leukoc Biol 2005; 77: 3–15.

17. Kellum JA, Kong L, Fink MP, et al. Understanding the inflammatory cytokine response in pneumonia and sepsis: results of the genetic and inflammatory markers of sepsis (GenIMS) study. Arch Intern Med 2007; 167: 1655–1663.

18. Estella A and Jareño A. Systemic inflammatory cytokine-mediated response after bronchoalveolar lavage in mechanically ventilated patients with suspected pneumonia. J Bronchology Interv Pulmonol 2012; 19: 102–108.

19. McBride WT, Armstrong MA and McBride SJ. Immunomodulation: an important concept in modern anaesthesia. Anaesthesia 1996; 51: 465–473.

20. Jawan B, Kao YH, Goto S, et al. Propofol pretreatment attenuates LPS-induced granulocyte-macrophage colony-stimulating factor production in cultured hepatocytes by suppressing MAPK/ERK activity and...
NF-kappaB translocation. *Toxicol Appl Pharmacol* 2008; 229: 362–373.
21. Steurer M, Schläpfer M, Steurer M, et al. The volatile anaesthetic sevoflurane attenuates lipopolysaccharide-induced injury in alveolar macrophages. *Clin Exp Immunol* 2009; 155: 224–230.
22. Sugasawa Y, Yamaguchi K, Kumakura S, et al. Effects of sevoflurane and propofol on pulmonary inflammatory responses during lung resection. *J Anesth* 2012; 26: 62–69.
23. Tschaikowsky K, Ritter J, Schröppel K, et al. Volatile anaesthetics differentially affect immunostimulated expression of inducible nitric oxide synthase: role of intracellular calcium. *Anesthesiology* 2000; 92: 1093–1102.
24. Peterson PK, Sharp B, Gekker G, et al. Opioid-mediated suppression of interferon-gamma production by cultured peripheral blood mononuclear cells. *J Clin Invest* 1987; 80: 824–831.
25. Wang CM, Tang RB, Chung RL, et al. Tumor necrosis factor-alpha and interleukin-6 profiles in children with pneumonia. *J Microbiol Immunol Infect* 1999; 32: 233–238.