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Infection v. colonisation

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Abstract. The interaction between bacteria and the human respiratory tract is complex and while the concept of three states, namely sterility, colonisation, and infection is clinically convenient it is inevitably in oversimplification. Evidence from both clinical and laboratory observations has led to some ideas about the relationship between colonisation and infection and while these are helpful in defining the steps involved, the decision of whether and when to start new treatment remains one of clinical judgement. This article reviews the evidence from lung disease both in and out of an intensive care unit and attempts to define the frontier between infection and colonisation in different clinical settings.

Key words: Infection – Colonisation – Bacterial adherence – Intensive care

Sterility to infection (Fig. 1)

Sterility to colonisation

Attempts have been made to trace the sequence of events at different sites in the human airway during intensive care which lead from sterility of the lower respiratory tract to frank clinical infection [1–3]. At the outset the upper airways and oropharynx are colonised with commensals while the trachea and distal airways are sterile. The first stage involves colonisation of the upper airways with potential pathogens (usually aerobic gram negative bacteria) with a subsequent increase in bacterial numbers [4]. This is followed by aspiration of organisms into the lower respiratory tract which then becomes colonised and again bacterial numbers increase, especially when clearance mechanisms are impaired. Finally the combination of deeper aspiration, larger numbers of bacteria and inflammation result in clinical infection. Each stage in this sequence is facilitated by both local and systemic factors which reduce host defences (Table 1) and the final event is characterised by local organ dysfunction and both local and systemic evidence of inflammation.

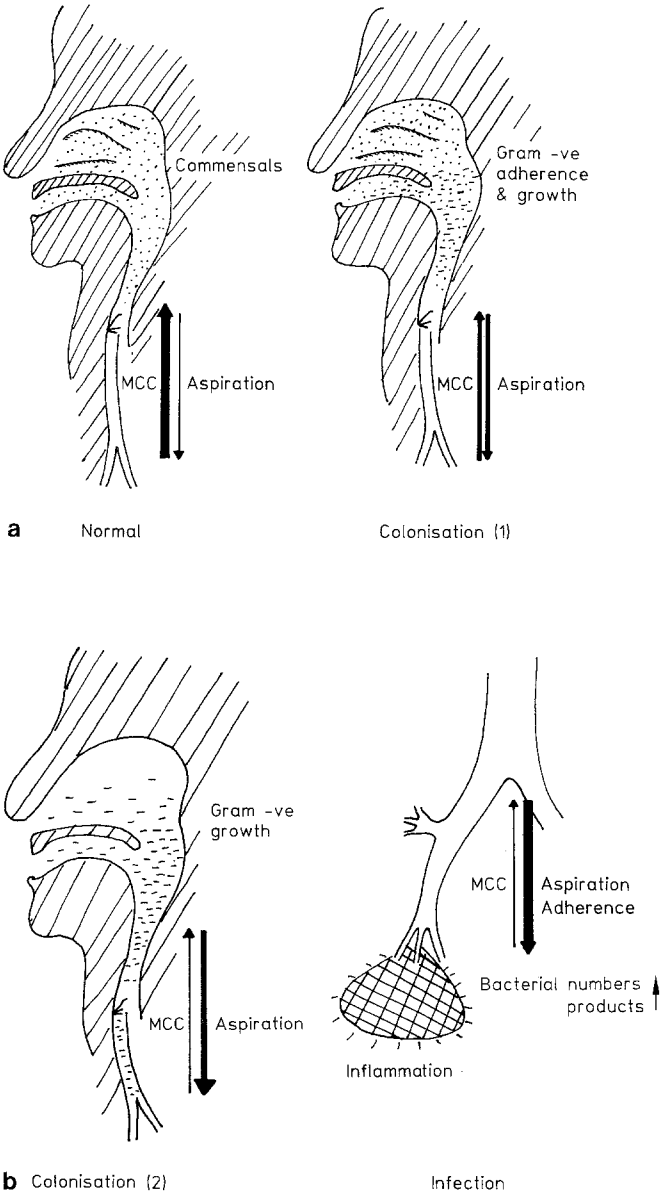

Fig. 1. See text

Table 1. Factors associated with lower respiratory tract infections in ITU

Local	Systemic
Previous lung disease	Malnutrition
Airway trauma	Trauma
Impaired clearance	Acidosis
	Uraemia
	Immune deficiency

Although there is good evidence to support each proposed step in this sequence there are also problems. In the first place the organisms which colonise the oropharynx are not necessarily those which cause pneumonia. Secondly, aspiration from upper to lower respiratory tract may be quite a common event without any sequelae [5]. It is also likely that some pneumonias develop from a single aspiration of a nidus of infection without going through this sequence. Similarly, this scheme does not fit all clinical situations and especially the more unusual infections in the immunosupressed host with AIDS or haematological malignancy.

From colonisation to infection

Although the two ends of the spectrum from colonisation to frank infection are quite easy to define both clinically (see below) and histologically, the middle of the spectrum is less well understood. Both bacterial and host factors are involved and the interaction between the two determine the position on the spectrum. The greater the number of bacteria, the more exotoxin production and the more tissue invasion the closer the situation is to frank infection. In response to these changes host immune and inflammatory responses may gain the upper hand and either eradicate the organisms or limit bacterial growth and so maintain a state of colonisation. Alternatively host responses may increase in parallel with bacterial growth to provide much of the local and distant signs of infection. It is unlikely that either bacterial or host factors represent a simple continuum but rather that negative feedback systems maintain a state of colonisation until an unstable equilibrium is reached when positive feedback develops to allow the second state of infection to develop. The transition from one state to the other may therefore be rapid and catastrophic. It is easy to visualise, for example, how bacterial adherence and growth may proceed to the point when neutrophils are attracted resulting either in bacterial killing and maintenance of low levels of colonisation (negative feed back) or in bacterial and neutrophil production of protease and ciliary dyskinetic factors, exposure of epithelial surface receptors, reduction in mucociliary clearance and so increased colonisation (positive feed back) (Fig. 2). Similar theoretical systems can be devised for many other bacteria/host interactions. The chief variables in this balance are bacterial adherence, mucociliary clearance and the local inflammatory and immune reactions.

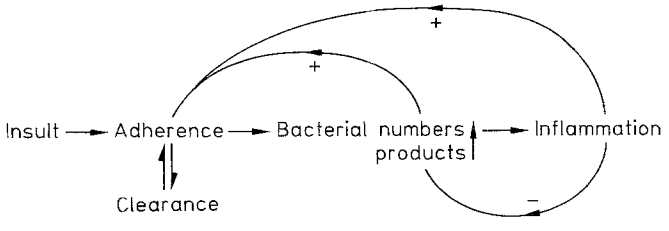

Fig. 2. Positive and negative feed back loops in lung inflammation

Bacterial colonisation

The original studies of Johanson [6] showed that colonisation of the oropharynx by gram-negative bacteria was rare in healthy normal subjects (6%) but increased with severity of illness (moderately ill 35%, severely ill 73%) and length of time in hospital. Such colonisation was found to be particularly frequent in patients receiving intensive care and was associated with coma, hypotension, intubation, acidosis, uraemia and an abnormally high or low circulating white count. In short, the iller the patient the more likely was oropharyngeal colonisation. Patients developing nosocomial pneumonia had a particularly high frequency of oropharyngeal colonisation and aspiration of these gram negative organisms was proposed as the cause together with diminished clearance of lower respiratory secretions. Aspiration of upper respiratory secretions into the lower respiratory tract appears to be surprisingly common [5] (45% in normals) and increases with impaired conscious level to 100% with coma. Lower respiratory toilet is performed by a combination of mucociliary clearance and cough and both are impaired in severely ill patients.

Not all the facts fit this schema. In the first place the oropharynx is not the only potential site for the multiplication of bacteria with subsequent aspiration. Respiratory equipment has been implicated in some cases and while bacterial contamination often occurs it seems likely that the equipment is contaminated by the patient rather than the other way round. More difficult to explain is the difference in patterns of colonising organisms in the oropharynx and lower respiratory tract. Streptococci, Actinomyces and enteric gram-negative bacteria usually colonise the oropharynx while Pseudomonas species favour the lower respiratory tract. Thus, independent patterns of colonisation may be found in the oropharynx and tracheal secretions from the same patient, especially with a tracheostomy or endotracheal tube [7].

Bacterial adherence

Normally bacteria which come in contact with epithelial surfaces fail to establish residence and are moved on by local clearance mechanisms. The first step in colonisation is, therefore, the adherence to epithelial cells and the mechanisms involved have been studied for both buccal and ciliated respiratory epithelial cells. Attachment occurs between bacterial pili and fimbriae and epithelial cell surface receptors which commonly contain mannose, and animal studies have shown adherence to be facilitated by such adverse factors as cigarette smoke, starvation and renal infarction – so mimicking the clinical associations

favouring colonisation in man. Some tropism for different epithelial cells which reflects the clinical findings has also been shown with Pseudomonas species adhering better to ciliated than buccal epithelial cells [8]. Similarly rough colonies of Pseudomonas adhere more avidly than mucoid variants, and some association between pathogenicity of strains of mycoplasma and adherence has been shown. Human studies are largely confirmatory with the findings of increased Pseudomonas adherence to cells from patients with tracheal Pseudomonas colonisation or with chronic tracheostomies as well as an association between adherence and poor nutrition.

The ways in which bacteria gain access to the cell surface receptors are also being intensively studied. In the normal situation these receptors are probably protected by mucins which together with IgA and other proteins may also prevent adherence by binding to the bacterial adhesins. These local defences may be breached by virus infection or by the products of local inflammation. For example proteases released by inflammatory cells (chiefly neutrophils and macrophages) can remove the protective fibronectin and so expose epithelial cell surface receptors which are then available for further bacterial adherence. Similarly proteases may break down IgA and so impair this mechanism of blocking adherence. Another important local defence against adherence may be surface charge. A reduction in mouth pH in xerostoma is associated with increased buccal colonisation and in tracheal cells from patients with tracheostomies the local pH similarly effects the adherence of Pseudomonas. It is interesting to note that the airway surface normally carries a charge of -5 to -30 mV with the highest charges in the proximal airways. This charge is abolished by viral infection and increased in cystic fibrosis, two situations favouring bacterial colonisation and infection.

Pulmonary clearance of bacteria

The fate of bacteria in the lung following aspiration depends on the balance between mucociliary clearance and bacterial killing on the one hand and bacterial multiplication on the other. Mucociliary clearance is particularly important in the airways (see below) while the balance between killing and growth is critical at the alveolar level. The first line defences responsible for bacterial killing include the complement and macrophage phagocytosis systems while alveolar inflammation recruits granulocytes and promotes the immune response. Many of these defenses are impaired by factors listed in Table 1. Bacterial multiplication is favoured by a large inoculum size, (10^5organisms are easily cleared while 10^8organisms usually cause pneumonia in animal studies) and bacterial virulence factors such as a polysaccharide capsule (klebsiella and pneumococcus) and exoproducts e.g. Pseudomonas derived proteases.

Mucociliary clearance

In the severely ill patient cough frequency and effectiveness are reduced by impaired conscious level, instrumentation and drugs eg: opiates and sedatives. Normal

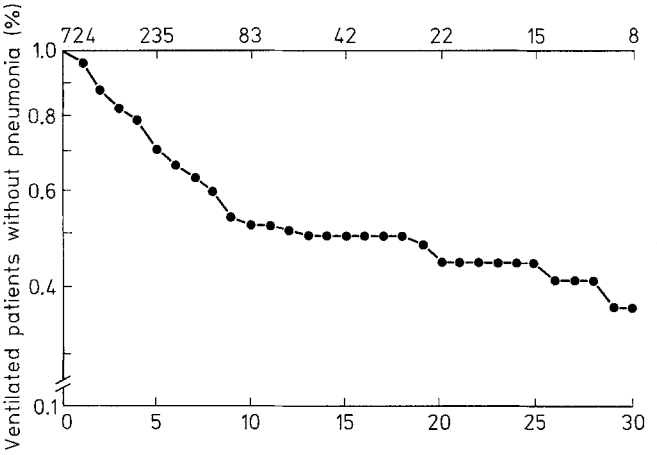

Fig. 3. Pneumonia and ventilator support (from [10])

mucociliary clearance depends on an intact ciliated epithelium, normal hydration of airway secretions which itself requires humidification of inspired gas as well as intact mechanisms of fluid and electrolyte transport across the epithelium, and optimum viscoelastic properties of airway mucus. Any or all these are often impaired in the ITU setting. The epithelium may be damaged by instrumentation, infection or inhaled gases; airway secretions may become dehydrated due to inadequate humidification of inspired gas as well as by disorders of epithelial transport, and mucus viscosity increases with dehydration and as a result of inflammation. Vicious cycles may develop whereby bacteria and the inflammation they provoke combine to reduce mucociliary clearance and so encourage further increase in bacterial numbers e.g.: H. influenzae and Ps. species both produce exoproducts which impair ciliary action.

Clinical observations

ITU

The above scheme has largely been worked out from the observation of respiratory tract infection in intensive care units. In this situation gram-negative colonisation of the oropharynx occurs early and tracheal secretions which may initially be sterile rapidly become colonised so that after one week of intubation and artificial ventilation almost all patients have positive cultures usually with Pseudomonas. Pulmonary infection occurs relatively frequently, especially in the first ten days (Fig. 3) and is predisposed to by the presence of multiple organ dysfunction as well as the factors listed in Table 1 [10]. Selective decontamination of the digestive tract with the aim of reducing the number of potentially pathogenic aerobes and yeasts while permitting colonisation by anaerobes together with systemic antibiotic therapy aimed at organisms which may have been present beforehand (e.g. *Streptococcus pneumoniae, Haemophilus influenzae*) is a logical approach for controlling colonisation and preventing infection and has been successful in some studies [11].

The fact that mortality following selective decontamination improves more in some patients groups (e.g. trauma) than others suggests that in the other clinical groups pneumonia develops as part of a general clinical deterioration and is seldom an independent cause of death.

Clinical diagnosis

The clinical differentiation between colonisation and infection depends upon the integration of information from many sources obtained in the course of frequent assessments of the patient. The aim is to recognise the transition from colonisation to infection early enough for prompt treatment to be effective before any organ function is impaired. The usual definition of an infection in this setting is based on the airway secretions and the chest X-ray, together with evidence of deteriorating pulmonary function as well as the presence of systemic changes.

Airway secretions

The transient presence of one or more organisms suggests simple contamination while persistant positive cultures of the same organism suggests colonisation. While attempts have been made to define the number of organisms present which indicate an infection (e.g. $>10^3$ cfu/ml) this is necessarily imprecise as the specimen may be diluted with saline used to irrigate the airways and delay in transport and processing by the laboratory will introduce errors. Nevertheless, large numbers of a single organism are more suggestive of infection than small numbers of a mixed bacterial growth. The value of bronchoalveolar lavage and bronchoscopic protected brush techniques as compared with tracheal aspirates have been evaluated and these provide improved specificity but similar sensitivity in the diagnosis of infections [12]. The appearances of the secretions gives some indication of infection and two chief variables are colour and viscosity. The more colourful the sputum along a spectrum of transparent white, yellow, light green, dark green, dark brown, the greater the likelihood of infection. Both the colour and the viscosity are largely a measure of the number of neutrophils present and so are an indication of the amount of local inflammation. However, any change in the appearance and volume in the respiratory secretions is an important early sign of infection.

The chest X-ray

A new infiltrate on the chest X-ray is often present during the development of a pulmonary infection in a ventilated patient. This is, however, an insensitive measure and in any case there are many other possible causes for an infiltrate in this clinical setting. Furthermore chest X-rays of ventilated patients may be difficult to read, and in patients with immune suppression the radiographic changes may be slight and delayed in the presence of a severe infection. The chest X-ray is therefore not a very valuable tool in diagnosis and treatment should not be delayed in order to wait for typical chest X-ray changes to develop.

Deteriorating pulmonary function

This may be shown as a deterioration in arterial blood gases, a change in the ventilatory requirements or in the patient showing discomfort on the ventilator. There are many different potential causes for such changes and deterioration in arterial blood gas may occur only after an infection is fully established. Such changes are therefore insensitive and like the chest X-ray, their absence should not cause a delay in treatment.

Systemic evidence of infection

The earliest sign may be a change in heart rate which can precede the development of a fever or an elevation in white cell count. An overall subtle change in the patients condition may be the earliest sign of all. Such a change may be noticed first by the patients regular attendants (physiotherapist, nurses) and consist of restlessness, fighting the ventilator together with minor changes in heart rate, blood pressure etc.

Other chest infections

A number of lung infections outside an intensive care unit also shed some light on the balance between infection and colonisation.

Chronic bronchitis

As a result of cigarette smoking a chronic state of mucus hypersecretion develops. The sputum varies from mucoid, which is usually sterile, to mucopurulent when *Haemophilus influenzae* with or without *Strep. pneumoniae* can be cultured with little local or systemic evidence of infection. While cigarette smoking continues this bacterial colonisation persists and probably does little damage to the lungs. From time to time a clinical infection develops, sometimes following a viral infection, but often related to climatic changes alone. The infection is associated with a brisk local and systemic inflammatory response which usually resolves spontaneously without sequelae and the patient returns to the previous state of chronic colonisation. In this situation cigarette smoke promotes and sustains colonisation rather than infection. A second insult involving disruption of epithelial cells, reduction in local defences and further impairment of clearance mechanisms all favour bacterial overgrowth and clinical infection. The important finding, however, is that the majority ($>80\%$) of such patients show no deterioration in lung function over many years in spite of chronic bacterial colonisation. This suggests a true state of colonisation with insufficient local inflammation to cause local tissue damage.

Cystic fibrosis

The inherited defect involves altered epithelial cell chloride permeability, increased sodium and water transport out of the airway lumen and, presumptively, dehydrated respiratory secretions. The surface electrical charge is abnormally negative. As a result the airways are colonised

early in childhood by Staphylococcus aureus and later by *Pseudomonas aeruginosa.* Although the patient may remain clinically well most of the time with a few infective exacerbations each year in a way that resembles the chronic bronchitic the consequences are quite different. The chronic bronchitic patient usually shows no deterioration in lung function with time, while such deterioration is uniformly seen in CF. The reasons for the difference are not known but the following may be important. In CF nutrition is also impaired and patients with well maintained weight also have the best lung function. Secondly, the volume and purulence of the sputum is greater in CF than chronic bronchitis and the bacterial colonising load is greater. Finally the organisms are different and Pseudomonas has particular propensity to produce exotoxins. All these factors are likely to put the patient with CF further along the spectrum between colonisation and infection as compared with chronic bronchitis with sufficient local inflammation to cause progressive tissue damage. Interestingly patients with CF very seldom develop pneumonia in spite of a high colonising load of Pseudomonas. This provides some insight into the relative importance of local protective mechanisms in the airways which are impaired in CF, a opposed to systemic immunity which is preserved.

Conclusions

The steps from sterility through colonisation to infection of the lower respiratory tract are becoming increasingly well understood. There is an important balance between bacterial adherence and growth on the one hand and host defences such as cough, mucociliary clearance and immune defences on the other. This balance may be struck at a number of different points in different clinical situations, but in ITU the change from one state to another can be very rapid. At present techniques of selective decontamination are promising as prophylaxis while early detection of the shift from colonisation to infection remains an important clinical skill in intensive care units.

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