

CHAPTER

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Colonization Versus Infection

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Introduction

There are many clinical situations when infection is suspected but tests do not reveal the causative organism. On the other hand sometimes an organism is isolated but it is difficult to decide whether it is a contaminant, colonizer or a true pathogen.

We live in a sea of microbes and so it is not surprising that microbes would contaminate clinical specimens and colonize almost all body surfaces. Hence surface specimens as well as those obtained by penetrating skin or a mucous membranes need careful interpretation.¹

Most organisms which colonize are harmless commensals and are best left alone. They may, in fact, prevent invasion by pathogens. This happens by competition for nutrition and by producing inhibitory metabolic products. Some commensals can nevertheless invade if they have an opportunity. It is important to remember that most pathogenic organisms set up colonization first and switch to an invasive mode after sensing a quorum¹ and suitable environmental conditions. These help them to fine tune expression of metabolic and resistance determinants. It is difficult but is critically important to pinpoint exactly when colonization turns to invasion.

Some common clinical scenarios which require this differentiation are : patients with burns, chronic

wounds like osteomyelitis with/without a draining sinus and diabetic foot ulcers, cultures from post-operative drains, positive urine cultures in an asymptomatic patient and in a catheterized patient, sputum/respiratory specimen showing organisms in a patient with suspected pneumonia, blood cultures in a patient with indwelling central venous catheter, arterial line, hemodialysis catheter.

The points which help distinguish colonization versus invasion are related to the findings at the site, the characteristics of the patient, the organism and on follow up.

Site

The normal skin and mucosae are home to a multitude of micro-organisms. Any breach in these linings provides them a chance of tissue invasion and thus produce disease. Micro-organisms attach to a foreign bodies and grow within biofilms in relation to them. These are situations where the identification of progression from colonization to invasion is important. An exposed wound or a site with a foreign body has a high likelihood of being colonized. Absence of clinical, imaging, biochemical or histological signs of invasion, inflammation and tissue reaction favors colonization. An organism which is isolated from a lesion in a normally sterile site like the CSF, blood, pleural fluid etc is likely to be a true invader and the causative pathogen. On

the other hand, an organism isolated from a non sterile specimen like sputum or a wound swab may be a colonizer. However it may be a true invader if grown in pure culture, or repeatedly, or is from a protected specimen, or has a colony count above certain specified limits.

Skin and soft tissue

In case of burns or chronic wounds, the local examination of the wound and the surrounding tissue provides valuable information for the clinician to decide whether the organism isolated is a colonizer or the true pathogen. A healthy, granulating wound with bleeding edges and normal surrounding tissue would warrant observation, rather than a specific antibiotic for the organism isolated from the wound swab. On the other hand, a "bad" wound would necessitate treating the organism isolated, preferably after obtaining more representative samples like deep wound swabs or deep tissue biopsy culture. In situations where there is loss of mucosal barrier (chemotherapy, severe drug reaction), the usual oral or gastro-intestinal flora may be expected to invade and cause disease.

Urine

In case of the urinary tract as a site of infection, the decision is made based on the colony counts of the organism, though there are fallacies in this too. UTI is diagnosed in² a non-catheterized patient based on symptoms, signs, pyuria, bacteriuria and the colony counts on urine culture. Normally, the upper urinary tract is sterile and the difficulty arises from collection of the specimen which may get contaminated with colonizers when passing through the lower urinary tract and urethra. Hence colony counts help in identifying patients who need treatment. Significant bacteriuria is defined as a single clean catch voided specimen with one bacterial species identified in a colony count of greater than or equal to 10^5 in men and the same count in at least 2 consecutive specimens in case of women. Positive urine cultures in an asymptomatic patient needs to be treated only in cases which require urological procedures and in pregnant

women. In a catheterized patient, it is difficult to evaluate for UTI symptoms or by pyuria which may be present due to instrumentation and persistent foreign body reaction. Urine cultures often grow organisms as the catheter is a common site for colonization. Hence, in these subsets of patients, it is necessary to differentiate colonization from infection to ascertain the need for treatment. A colony count of greater than or equal to 10^2 is defined as significant bacteriuria in a catheterized patient. Again, treatment of asymptomatic bacteriuria in the catheterized patient is not recommended, though if persisting beyond 48 hours of removal of the catheter, therapy may be considered.

Respiratory infections

Ventilator associated pneumonia is difficult to diagnose with certainty.³ An organism isolated from respiratory secretions could be a contaminant, commensal or the true pathogen. The etiological diagnosis is usually made based on semi-quantitative cultures⁴ as described - Tracheal Aspirate $> 10^5$; BAL $> 10^4$; Protected Brush Specimen $> 10^3$. Ten times less colony count is taken as significant in the presence of antimicrobials³. More than 5% intracellular bacteria in BAL fluid also signifies infection. But the positive predictive value (PPV) of these colony counts is poor. It is important to remember that a colony count of $< 10^5$ in the absence of antimicrobials has a good negative predictive value (NPV) in the diagnosis of pneumonia. Organisms may be isolated in a significant count even in a case of tracheo-bronchitis and thus the clinical syndrome and the radiological picture have to be correlated. In case of community acquired pneumonia, sputum examination may provide the clue to the etiological agent if the sample is representative of the lower respiratory tract i.e has more than 25 PMN and less than 10 epithelial cells per low power field. This assures that the organisms seen are not oral commensals. Absence of *S. aureus* or GNB in the sputum is a strong evidence against the presence of these pathogens, but mere presence is not sufficient evidence of infection. In the immunocompetent patient, organisms like *Aspergillus* and *Candida*

in the sputum may represent colonizers and warrant therapy only if there is evidence of invasive disease such as imaging, histopathology or fungal antigenemia.

Central venous catheter related infections

There are particular difficulties in distinguishing a colonized central venous catheter (CVC) from one responsible for catheter related blood stream infection (CRBSI).⁵

CRBSI is diagnosed when

1. Local or systemic manifestations are present and the sample obtained from the CVC shows 5-10 times more CFU than the percutaneously obtained blood sample, or
2. The differential time to positivity is > 2 hours or
3. > 10² CFU are obtained from a tunneled catheter without a companion culture from a percutaneous site or
4. > 15 colonies or > 10² CFU are obtained from culture of the catheter tip

CRBSI is indicated with a PPV 60-70%, but the NPV is higher at 98%.

Thus a negative catheter related sample rules out CRBSI better than a positive sample indicating one.

When the blood culture obtained from the catheter is positive but the percutaneous blood sample is negative, its true significance is unknown. It may indicate colonization of the catheter rather than CRBSI especially when the isolated organism is a gram negative rod or enterococcus. However, if the organism is *S. aureus* or *Candida*, or if patient has valvular heart disease or neutropenia close monitoring is required which includes evaluation for infective endocarditis and metastatic infection.

Patient

A patient from whom an organism is isolated, has received multiple antibiotics for a prolonged period, has no compatible syndrome or has an alternative

explanation for the clinical signs and symptoms is likely to be colonized rather than truly infected. *Candida* is frequently isolated from sputum, tracheal secretions and BAL, especially in antibiotic treated patients is almost always a colonizer. This colonization by *Candida* is best considered as a risk factor rather than as a disease. Isolation of organisms from an immuno-compromised patient has greater importance than isolating the same organism in a immuno-competent patient. e.g *Aspergillus* from respiratory specimen or *Candida* from urine.

Organism

Some organisms are known from prior experience to be frequent colonizers or contaminants of specimens obtained through skin or instruments that are difficult to sterilize or of flushing solutions. e.g. Coagulase Negative Staphylococcus (CoNS), Non-Tuberculous Mycobacteria (NTM). These should be considered as colonizers except in special clinical situations like repeated isolation of CoNS from blood in the presence of a foreign device or of NTM from respiratory samples in a patient with a compatible clinical condition for NTM disease like COPD, or smoking. Candiduria in a patient with a urinary catheter poses a clinical dilemma: to treat or not to treat. While *Candida* in the urine may be a colonizer, it can be the first indication of fungemia. Urinary *Candida* colony counts, unfortunately, do not help to sort out this situation. Candiduria should be treated if the patient has symptoms, has neutropenia, is a renal transplant recipient, is due to undergo urologic procedures or is a low birth weight infant.⁶

On the other hand, even one blood culture positive for *Candida* indicates tissue invasion. This has high risk of mortality, but the sensitivity of blood culture is only 50%. Hence there is a great need to identify patients at high risk of Candidemia in the critical care setting. One way to do this is by surveillance cultures of oropharynx, stomach, rectum, trachea, urine, catheter tips and surgical drains. Colonization may turn into invasion if a large proportion of these sites are heavily colonized.

Beta-Glucan testing also offers an opportunity to distinguish colonization versus infection with the two sequential positive results having a high specificity for diagnosis of invasive disease.⁷ High APACHE score also predicts invasion by *Candida* in a significant number of patients.

Some organisms are never colonizers and always represent true infections. When found in sputum, organisms like MTB, RSV, influenza, parainfluenza, *Legionella*, *Chlamydia*, *Cryptococcus*, *Pneumocystis*, *Strongyloides* are considered as pathogens and not as mere colonizers.⁸ Similarly, when found in stool, *Salmonella* are always considered as pathogens.

Follow Up

If the organism is persistently isolated despite 'effective' systemically administered therapy, it is likely to be a colonizer as it is not 'seeing' the antibiotic. If it is persistently isolated despite clinical improvement it is obviously not responsible for the patient's clinical picture. In fact, appropriate follow up is very important as it would prove or disprove his earlier clinical judgement. Hence, close monitoring of the patient both local and systemic signs and symptoms of tissue invasion is very essential.

Distinguishing colonization and invasion is of paramount importance. The clinician may treat the colonizer unnecessarily, generating antimicrobial resistance while missing the true pathogen or the non infectious disease. The patient encounters toxicity, interactions and increased cost. On the other hand the clinician may dismiss the organism as a colonizer when invasion is imminent or has already occurred, thus leading to treatment delay which is a powerful contributor to an adverse outcome.

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